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Proposed Re-evaluation Decision PRVD2017-16

Dichlorvos and Its Associated End-use Products

Consultation Document

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6607 D
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca

Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Table of Contents

Proposed Re-evaluation Decision 1
  Outcome of Science Evaluation 1
  Proposed Regulatory Decision for Dichlorvos 2
  International Context 3
  Next Steps 4
  Additional Scientific Information 4
Science Evaluation 7
1.0 Introduction 7
2.0 Technical Grade Active Ingredient 7
  2.1 Identity 7
  2.2 Physical and Chemical Properties 8
3.0 Human Health Assessment 8
  3.1 Toxicology Summary 8
    3.1.1 *Pest Control Products Act* Hazard Characterization 22
  3.2 Dietary Exposure and Risk Assessment 23
    3.2.1 Determination of Acute Reference Dose 23
    3.2.2 Acute Dietary Exposure and Risk Assessment 24
    3.2.3 Determination of Acceptable Daily Intake 24
    3.2.4 Cancer Assessment 25
    3.2.5 Chronic Dietary Exposure and Risk Assessment 25
  3.3 Exposure from Drinking Water 25
    3.3.1 Concentrations in Drinking Water 26
    3.3.2 Drinking Water Exposure and Risk Assessment 26
  3.4 Occupational and Non-Occupational Exposure and Risk Assessment 26
    3.4.1 Toxicology Endpoint Selection for Residential and Occupational Exposure 26
    3.4.2 Non-Occupational Exposure and Risk Assessment 27
    3.4.3 Occupational Exposure and Risk Assessment 30
  3.5 Aggregate Exposure and Risk Assessment 34
    3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment 34
    3.5.2 Residential, Non-Occupational and Dietary Aggregate Exposure and Risk Assessment 34
  3.6 Cumulative Assessment 35
  3.7 Incident Reports 35
4.0 Environmental Assessment 35
  4.1 Fate and Behaviour in the Environment 35
  4.2 Environmental Risk Characterization 37
    4.2.1 Risks to Terrestrial Organisms 38
    4.2.2 Risks to Aquatic Organisms 39
5.0 Value Assessment 40
6.0 Pest Control Product Policy Considerations 41
  6.1 Toxic Substances Management Policy Considerations 41
  6.2 Formulants and Contaminants of Health or Environmental Concern 42
7.0 Conclusion 42
List of Abbreviations 45

Appendix I 49
Table 1 Dichlorvos Products Registered in Canada as of 1 June 2017 Excluding Discontinued Products or Products with a Submission for Discontinuation Based on the PMRA's Electronic Pesticide Regulatory System (e-PRS) database 49
Table 2 Registered Commercial Class Uses of Dichlorvos in Canada as of 1 June 2017[1] 51
Table 3 Registered Domestic Class Uses of Dichlorvos in Canada as of 1 June 2017[1] 53
Appendix II Toxicological Information for Health Risk Assessment 55
Table 1 Toxicology Profile 55
Table 2 Toxicology Reference Values for Use in Health Risk Assessment for Dichlorvos . 83
Appendix III 85
Table 1 Dietary Exposure and Risk Estimates for Dichlorvos 85
Table 2 Dietary Exposure and Risk Estimates for Naled 85
Table 3 ARI's for Combined Dietary Risk from Dichlorvos and Naled 86
Appendix IV Food Residue Chemistry Summary 89
Appendix V Non-Occupational Risk Assessment 91
Table 1 Postapplication Inhalation Exposure and Risk Assessment for Pest Strips 91
Table 2 Postapplication Inhalation Exposure and Risk Assessment for Outdoor Mosquito Control in Residential Areas 91
Table 3 Postapplication Inhalation Exposure and Risk Assessment for Theaters and Animal Barns 92
Appendix VI Commercial Mixer/Loader/Applicator Risk Assessment 93
Table 1 Mixer/Loader/Applicator Exposure and Risk Assessment of Dichlorvos in Greenhouses 93
Table 2 Mixer/Loader/Applicator Exposure and Risk Assessment of Dichlorvos in Structures 93
Table 3 Mixer/Loader/Applicator Exposure and Risk Assessment of Dichlorvos in Human Habitat and Residential Outdoors 95
Appendix VII Postapplication Worker Risk Assessment 97
Table 1 Combined Postapplication Greenhouse Risk Assessment 97
Table 2 Postapplication Risk Assessment for Structural Sites based on the USEPA Model in Food Processing Plants 98
Appendix VIII Aggregate Risk Assessment 99
Table 1 Aggregate Risk Assessment for Theaters and Animal Barns 99
Appendix IX Environmental Assessment 101
Table 1 Physico-chemical Properties of Dichlorvos 101
Table 2 Summary of Abiotic Transformation Processes of Dichlorvos 101
Table 3 Summary of Biotic Transformation Processes of Dichlorvos 103
Table 4 Summary of Mobility of Dichlorvos 105
Table 5 Acute, Dietary, and Chronic Toxicity of Dichlorvos to Birds and Mammals 105
Table 6 Acute Toxicity of Dichlorvos to Aquatic Invertebrates 108
Table 7 Chronic Toxicity Endpoints for Freshwater Invertebrates 109
Table 8 Acute Toxicity of Dichlorvos to Freshwater Fish 109
Table 9 Acute Toxicity of Dichlorvos to Marine Aquatic Invertebrates 110
Table 10 Acute Toxicity of Dichlorvos to Marine Fish 112

Table 11 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria 112
Appendix X Label Amendments for Products Containing Dichlorvos 115
References 121

Proposed Re-evaluation Decision

Under the *Pest Control Products Act*, all registered pesticides must be regularly re-evaluated by Health Canada's Pest Management Regulatory Agency (PMRA) to ensure that they continue to meet current health and environmental safety standards and continue to have value. The re-evaluation considers data and information from pesticide manufacturers, published scientific reports, and other regulatory agencies. The PMRA applies internationally accepted risk assessment methods as well as current risk management approaches and policies.

Dichlorvos is a broad spectrum, non-systemic organophosphate insecticide used to manage various insect pests on: greenhouse cucumbers, tomatoes and ornamentals, indoor and outdoor structural sites (for example, processing plants, storage facilities, livestock housing and outdoor recreational areas) and for mosquito control. Dichlorvos is applied indoors by hand sprayers, ultra-low volume applicators, and automatic foggers, as well as used in insecticide strips. It is applied outdoors by ground equipment. It is registered for both commercial and domestic uses.

This document presents the proposed regulatory decision for the re-evaluation of dichlorvos including the proposed risk mitigation measures to further protect human health and the environment, as well as the science evaluation on which the proposed decision was based. All products containing dichlorvos registered in Canada are subject to this proposed re-evaluation decision. This document is subject to a 90-day public consultation period, during which the public including the pesticide manufacturers and stakeholders may submit written comments and additional information to the PMRA. The final re-evaluation decision will be published taking into consideration the comments and information received.

Outcome of Science Evaluation

Dichlorvos provides consistent and effective control of a range of economically important insect pests on greenhouse crops and indoor and outdoor structural sites. The low persistence of dichlorvos makes it a very useful tool in greenhouse tomato, cucumber and ornamental integrated pest management programs, where it is effective for end-of-season control of insect pests between crop cycles before the introduction of beneficial insects. Dichlorvos is important for controlling cigarette beetle and tobacco moth infestation in stored tobacco due to its level of efficacy against these pests. The volatility of dichlorvos adds to its effectiveness in the domestic and commercial insecticide strips. It is fast-acting and compatible with integrated pest management practices when used in conjunction with pheromones in insect traps to monitor insect pest populations in fruit and vegetable crops.

With respect to human health, risks of concern were identified for some residential and occupational exposures to dichlorvos. Therefore, cancellation of uses for greenhouse cucumbers and tomatoes, greenhouse cut flower ornamentals, outdoor mosquito control, outdoor residential living areas, and indoor pest strips (excluding areas that are unoccupied for a minimum of 4 months) is proposed. Mitigation measures are required for all remaining uses. Exposure from the remaining uses is unlikely to affect human health when used according to the proposed label directions.

Dichlorvos enters the environment when used to control insects in and around human habitation and other outdoor living spaces, or when it is present in water discharges from use in greenhouses and mushroom houses. When used according to the proposed label directions, dichlorvos is not expected to pose risks of concern to the environment.

Proposed Regulatory Decision for Dichlorvos

Under the authority of the *Pest Control Products Act* and based on the evaluation of currently available scientific information, Health Canada is proposing that certain products containing dichlorvos are acceptable for continued registration for sale and use in Canada, provided that the risk mitigation measures are in place.

Registered pesticide product labels include specific directions for use. Directions include risk mitigation measures to protect human health and the environment that must be followed by law. As a result of the re-evaluation of dichlorvos, further risk mitigation measures for product labels are being proposed.

Human Health

To protect homeowners and those entering treated areas, the following proposed risk mitigation measures are required.

For Domestic-class products:

- Label statements prohibiting the use of pest strips in any area of an inhabited home, including in attics, crawl spaces, and garages.
- Label statements prohibiting use of pest strips in commercial areas, including animal and other farm buildings, milk rooms, motels, restaurants, food processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces.
- Restriction of domestic pest strips to structures that are continuously unoccupied for a minimum of 4 months (for example, cottages closed for the winter).

For Commercial-class products:

- For use with automatic application equipment only and a 4-day restricted-entry interval with full ventilation for greenhouse potted ornamentals, tobacco storage, animal buildings, food processing plants, industrial plants, warehouses, and theaters.
- Restriction on amount handled per day for tobacco storage, food processing plants, industrial plants, warehouses, and theaters (limited to 1.14 kg a.i./day).
- Additional required label statements

The following uses pose risks of concern to human health and do not meet Health Canada's current standards for human health protection. As a result, these uses are proposed to be cancelled:

- greenhouse tomato and cucumber, and greenhouse ornamentals (excluding greenhouse potted ornamentals),
- outdoor mosquito control,
- outdoor residential living areas, and
- indoor pest strips (excluding areas that are unoccupied for a minimum of 4 months).

The use in mushroom houses was not supported by dichlorvos registrants, and was not included in this re-evaluation. Therefore, this use is proposed to be removed from the product labels.

Residue Definition for Enforcement:

- The current residue definition for dichlorvos is dichlorvos *per se* for enforcement purposes. No change to the residue definition for enforcement purposes is being proposed. Dichlorvos is a metabolite and degradation product of naled, a registered pesticide. For risk assessment purposes, dichlorvos from all sources, including dichlorvos resulting from the use of naled were considered. In addition, since dietary exposures from naled and dichlorvos can co-occur and since they have a common toxic effect (cholinesterase inhibition), a risk assessment from combined exposures to both dichlorvos and naled was conducted.

Environment

To protect the environment, the following proposed risk mitigation measures are required:

- Hazard statements on the label to inform the user that dichlorvos is toxic to pollinators, beneficial arthropods, birds, mammals, and aquatic organisms. For uses where pollinator and beneficial arthropod species could be exposed, label statements must advise to avoid application during periods of bloom, and when bees and other beneficial insects are used in greenhouses. In addition, during the phase-out of the use of mosquito fogging , or should this use remain registered after public consultation, statements indicating that applying during cooler hours of the night and early morning reduces exposure to foraging bees and beneficial insects are required.
- A label statement to inform the user to not discharge dichlorvos-contaminated effluent from greenhouses into aquatic environments.
- Label statements informing users of ways to reduce the potential for runoff will be required.

International Context

Dichlorvos is currently acceptable for use in other Organisation for Economic Co-operation and Development (OECD) member countries, including the United States. Dichlorvos is under registration review by the United States' Environmental Protection Agency.

Due to health and environmental concerns, dichlorvos is no longer approved for sale or use in plant protection products in the European Union as per European Commission regulation 1100/2009.

Next Steps

The public including the registrants and stakeholders are encouraged to submit additional information that could be used to refine risk assessments during the 90-day public consultation period[1] upon publication of this proposed re-evaluation decision.

All comments received during the 90-day public consultation period will be taken into consideration in preparation of re-evaluation decision document[2], which could result in revised risk mitigation measures. The re-evaluation decision document will include the final re-evaluation decision, the reasons for it and a summary of comments received on the proposed re-evaluation decision with the PMRA's responses.

Additional Scientific Information

The science evaluation of dichlorvos considered chemical/scenario specific information for many uses provided by the registrants and stakeholders through consultations. Therefore, no additional data are required at this time. However, certain areas of the occupational and/or residential exposure and risk assessment relied on the current label information only. Therefore, additional information in these areas may further refine the occupational and/or residential exposure and risk assessment, which in turn, could potentially result in maintaining certain uses that are proposed for cancellation.

For greenhouse cucumber, tomato, and/or greenhouse cut flower ornamentals:

- Additional use information on how and when dichlorvos is used in greenhouses
- Depending on how this information impacts the risk assessment, chemical-specific dislodgeable foliar residue data in greenhouses and air monitoring data in greenhouses may also be useful for further refinement.

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[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[2] "Decision statement" as required by subsection 28(5) of the Pest Control Products Act.

For outdoor mosquito control and outdoor residential living areas:

- To refine the handler assessment, use pattern information (that is, amount treated per day to potentially refine area treated per day in the handler assessment)
- Depending on how this information impacts the risk assessment, chemical-specific passive dosimetry study or biological monitoring with acceptable human pharmacokinetic data for applicators may also be useful for further refinement.
- To refine the postapplication exposure assessment, chemical-specific air monitoring data and transferable residue data.

Science Evaluation

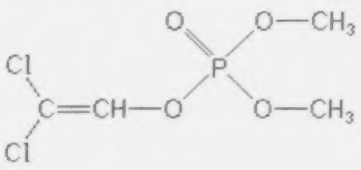
1.0 Introduction

Dichlorvos is a broad spectrum, non-systemic organophosphate insecticide that when applied, rapidly reduces pest populations. It works by contact, ingestion (stomach poison) and vapour action, specifically by inhibiting the enzyme acetylcholinesterase. Dichlorvos belongs to the Resistance Management Mode of Action group 1B, as classified by the Insecticide Resistance Action. Dichlorvos is used in agriculture, structures and outdoor areas to control various insect pests. Appendix I, Table 1 lists all dichlorvos products that are currently registered under the authority of the *Pest Control Products Act* as 1 June 2017. Appendix I, Table 2 lists all Commercial Class uses for which dichlorvos is registered. Unless otherwise indicated, these uses were supported by the registrants at the time of re-evaluation initiation and were therefore considered in the health and environmental risk assessments of dichlorvos. Appendix I, Table 3 lists all Domestic Class uses for which dichlorvos is registered.

Following the re-evaluation announcement for dichlorvos, the registrant indicated support to continue registration of all uses included on the labels of dichlorvos end-use products with the exception of the use in mushroom houses. As this use was not supported by the registrant, it was not included in this re-evaluation.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name		Dichlorvos
Function		Insecticide
Chemical Family		Organophosphate
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	2,2-dichlorovinyl dimethyl phosphate
2	**Chemical Abstracts Service (CAS)**	2,2-dichloroethenyl dimethyl phosphate
CAS Registry Number		62-73-7
Molecular Formula		$C_4H_7Cl_2O_4P$
Structural Formula		

Molecular Weight	221.0
Purity of the Technical Grade Active Ingredient	97.7%
Registration Number	19723

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	2.1×10^3 mPa
Ultraviolet (UV) / visible spectrum	Not expected to absorb at $\lambda > 250$ nm
Solubility in water at 25°C	18 g/L
n-Octanol/water partition coefficient	Log K_{ow} = 1.9, 1.42 (different studies)
Dissociation constant	N/A

3.0 Human Health Assessment

3.1 Toxicology Summary

The toxicology database for dichlorvos is based on unpublished laboratory studies, studies from the published scientific literature and reviews conducted by various international regulatory authorities. Notwithstanding, the amount of high-quality toxicology data on dichlorvos is limited; however, the available information was relied upon to establish endpoints for risk assessment purposes.

Following oral exposure in rats, dichlorvos was rapidly absorbed via the gastrointestinal tract. Peak concentrations in blood occurred within 15 minutes to 1 hour post-dosing. Urine and expired air were the major excretion routes for radioactivity following single high-dose administration in rodents, with faeces being a minor route of excretion. Dichlorvos was also excreted via expired air in orally-dosed humans.

Metabolites were widely distributed in rat tissues following oral exposure to radiolabelled dichlorvos with the highest concentrations in the liver, kidneys, uterus, spleen, gastrointestinal tract, skin and lungs. Lower concentrations were noted in bone, blood, brain, fat, heart and muscle. Residual radioactivity was detected up to 7 days post-dosing in the bone, kidney and liver.

Dichlorvos was rapidly converted into various metabolites with no unchanged dichlorvos excreted. Major urinary metabolites in laboratory animals included dimethyl phosphate, monomethyl phosphate, dichloroethyl glucuronide, desmethyldichlorvos, hippuric acid and urea, while minor urinary metabolites included S-methyl-L-cysteine oxide, 2,2-dichloroethyl-β-D-glucopyranosiduronic acid and methyl-mercapturic S-oxide. Hippuric acid and urea were also identified as minor fecal metabolites. Metabolic and excretion profiles were generally similar across species, with the exception of desmethyl dichlorvos which was a major metabolite in the mouse but not in the rat.

When administered via inhalation, dichlorvos generally had a similar kinetic and metabolic profile in rodents as when administered orally although 2,2-dichloroethyl-β-D-glucopyranosiduronic acid was identified only in the oral study as a major metabolite. Dichlorvos was not detectable in tissues following repeat low-dose exposures via inhalation. The only notable sex differences were with respect to the concentration of unchanged dichlorvos identified in the kidney, where males had a significantly higher concentration than females following a single high-dose inhalation exposure. In humans, unchanged dichlorvos was not detected in the blood after inhalation exposure and dichlorethanol was identified as a urinary metabolite.

In multiple species of laboratory animals, dichlorvos was highly acutely toxic when administered by the oral and dermal routes and was moderately toxic via inhalation. All species tested responded similarly to the acute effects of orally and dermally administered dichlorvos, although the rabbit appeared to be more sensitive by the oral route of exposure as compared to other species. Clinical signs associated with acute toxicity included cholinergic effects. Acute lethality was associated with respiratory failure and necropsy findings in the lung, liver, kidney, spleen, lungs, thymus, gastrointestinal tract, cardiovascular system, bladder and muscle.

Dichlorvos was classified as a severe eye irritant and was systemically toxic via the ocular route in rabbits, producing both cholinergic signs and mortality. Mortality and cholinergic signs were also noted in dermal irritation assays in rabbits along with slight skin irritation. Dichlorvos was a dermal sensitizer in a guinea pig maximization assay.

Repeat-dose administration of dichlorvos by the oral route (primarily gavage studies) identified inhibition of cholinesterase as one of the most sensitive toxicological parameters. Other effects included a variety of cholinergic clinical signs, behavioural changes, decreases in red blood cell parameters and white blood cell counts, body weight effects and alterations in organ weights, liver enzymes, liver pathology and functional observational battery (FOB) measurements. There did not appear to be any sex-specific differences in susceptibility nor were there any identifiable differences in species sensitivity. The dichlorvos database was inadequate for drawing definitive conclusions concerning comparative toxicity with gavage versus dietary administration; however, based on metabolism data and the general characteristics of organophosphate intoxication, it is likely that dichlorvos would be more toxic with gavage administration.

With respect to repeated dermal exposure, the toxicology studies for dichlorvos were inadequate in terms of the quality of information available. No NOAELs were established in any mammalian dermal study. Effects occurring at the lowest observed adverse effect levels (LOAELs) in these studies consisted of cholinergic clinical signs and cholinesterase inhibition. The available data, though of limited usefulness, suggested that dichlorvos was highly toxic with repeat-dose dermal administration.

Although the database for repeat-dose inhalation studies was also inadequate, the available data indicated that cholinesterase inhibition was likely the most sensitive toxicological endpoint by this route. In terms of route-specific effects, dichlorvos appeared to be at least as toxic, if not more toxic, via inhalation compared to administration via oral gavage. Other toxic effects associated with low-dose inhalation exposure included decreased body weight, heart, kidney and spleen weight, increased liver enzymes and mortality.

A six-week gavage immunotoxicity study in rabbits demonstrated inhibition of cholinesterase activity as the most sensitive toxicological parameter. Cholinesterase inhibition was noted at the low-dose level after one week of exposure. At a higher dose level, a treatment-related decrease in immune function was noted based on a significant suppression of humoral immune response and of cell-mediated immunity.

Dichlorvos was shown to induce neurofunctional effects in rats and hens. These effects were reversible and consisted of a variety of cholinergic signs and changes in FOB parameters. In hens, equivocal evidence of acute delayed neurotoxicity and neuropathology was observed. The incidence of neuropathological findings was low in the acute study and consisted of degeneration of the proximal sciatic nerve with axonal swelling in the proximal and distal parts of the nerve. In the repeat-dose delayed neurotoxicity study, effects included degeneration of the sciatic nerve, tibial nerve, cerebellum and spinal cord and thickening or densely staining material within the myelin; however, no changes in the brain or spinal cord neuropathy target esterase (NTE) were detected. In 3-month oral toxicity studies in the rabbit and rhesus monkey, electron microscopy revealed changes in the neuromuscular junction consisting of a reduction in synaptic vesicles and disarrangement of myofilaments.

Neurophysiological effects occurring at doses above those resulting in cholinesterase inhibition were observed in high-dose acute studies and in low-dose subchronic (up to 90 days) studies in rats. These effects included alterations in electroencephalogram (EEG) and electrocardiogram (ECG) measures as well as reduced conduction velocity of the tail nerve.

In utero and lactational exposure of rats to dichlorvos also resulted in several alterations in EEG parameters in 12-week old offspring. It was unclear from this published study whether offspring were also exposed to dichlorvos postweaning, thus limiting the ability to draw conclusions regarding sensitive pathways or life stages.

A 2-generation reproductive toxicity study in the rat in which dichlorvos was administered in drinking water resulted in reproductive and offspring effects at levels causing inhibition of cholinesterase activity in maternal animals. Reproductive effects included decreases in fertility and pregnancy indices and the number of dams bearing litters as well as increases in females with abnormal estrous cycling. Offspring effects included slight decreases in pup weight and pup survival. Offspring cholinesterase activity was not measured but cholinergic signs of toxicity were not observed in the offspring at the dose levels tested. Dichlorvos was also shown to cross the placental barrier and enter fetal circulation in rabbits. In an in vitro study, dichlorvos demonstrated very weak anti-androgenic activity.

In developmental toxicity studies, dichlorvos was not teratogenic in any of the species tested (rats, mice and rabbits) following gavage dosing. Maternal animals were more sensitive than their fetuses to the toxic effects of dichlorvos in developmental toxicity studies. Effects in maternal animals consisted of cholinesterase inhibition, tremors, clinical signs and mortality as well as decreased activity, body weight gain, food consumption, food efficiency and liver weight. Fetal effects in the developmental toxicity studies were limited to slight decreases in body weight. Even though the developmental toxicity studies had some limitations, for example, low animal numbers, dosing errors, lack of cholinesterase measurements, collectively, they were considered adequate since all of these studies demonstrated a lack of teratogenicity and fetal sensitivity.

In a gavage developmental neurotoxicity (DNT) study, maternal findings were limited to one high-dose female sacrificed on lactation day (LD) 3 due to clinical signs of toxicity. There were no treatment-related effects on maternal body weight, FOB parameters or gestation length but there were two total litter resorptions at the high-dose. During postnatal days (PNDs) 1 to 5, pup mortality was elevated along with a high percentage of whole litter losses in all groups including controls. Thus, the number of litters available for assessment in this dose group was low as was the confidence in the ensuing offspring assessment. Although there were minimal observations in the offspring FOB assessment, the methodology was lacking a full description of how effects could be differentiated from normal activity. Motor activity data were subject to large variations in sample size due to whole litter losses within the groups. In addition, there was a lack of habituation observed in the PND 22 animals and in PND 60 females at all dose levels including controls. The lack of habituation in controls raises concern for the validity and utility of this measure. Auditory startle reflex amplitude in PND 23 high-dose males was statistically significantly increased. Auditory startle reflex amplitude was also elevated (not statistically significantly) in the low- and mid-dose PND 23 males although not always in a dose-responsive manner; accordingly, the response was considered equivocal at these dosage levels. Water maze testing revealed lower percentages of successful trials relative to the straight swim channel times for high-dose males and females during the retention phase of this learning and memory task. Mid-dose PND 62 males also showed a lower percentage of successful trials during the retention phase. Examination of the brain morphometry data at the high-dose demonstrated an increased width of the hippocampus, dentate gyrus and piriform cortex along with a decreased height/thickness of the inner granular layer of the pre-pyramidal fissure and thalamus. It should be noted that no brain morphometric measurements were taken for the low- and mid-dose animals in this study. No treatment-related effects were noted on age at preputial separation/vaginal patency, brain weight or neuropathology.

In a second gavage DNT study, dichlorvos was administered to pregnant female rats at a single dose level to provide supplemental information to the previous study where a high number of whole litter losses were noted at this similar dose level. The same methodology as the previous study was used and the same parameters were investigated. No treatment-related deaths, clinical signs of toxicity or abnormal FOB findings were observed in any maternal animals during the study. Maternal body weight, pregnancy rate, and gestation length were similar between the treated and control groups. The results of this study were confounded by excessive litter loss in the control group like that observed in the previous study. In the control group, a total of five dams had whole litter loss during lactation and another eight litters had insufficient numbers of pups for selection of F_1 animals. Only two treated dams had whole litter loss. In the offspring available for evaluation, no treatment-related effects were observed on body weight, body weight gain, food consumption, developmental landmarks, FOB, motor activity, learning and memory, brain morphology or neuropathology. No treatment-related effect was noted on age at preputial separation or vaginal patency. As per the previous study, the description of the FOB methodology was limited and there was a lack of motor activity habituation observed in the PND 22 animals and in PND 60 males. An increase in absolute cerebellum weight was noted in PND 12 females. Auditory startle reflex amplitude was also elevated (not statistically significant) in the treated PND 23 males, but to a lesser degree than with the corresponding dose in the previous study.

Based on limitations in the two DNT studies, including the high pup mortality, lack of habituation in motor activity data and lack of brain morphometry measurements taken at the low- and mid-dose levels, these studies do not meet the guideline requirements. They do, however, provide supplementary information.

Rats were exposed by gavage to dichlorvos in a series of acute and repeat-dose cholinesterase inhibition studies. A benchmark dose (BMD) analysis was conducted to refine the effect levels and to determine if the young were more sensitive than adults with respect to the inhibition of brain and erythrocyte cholinesterase activity. Of the four available acute studies, only one examined different age groups of rats (PNDs 8, 15 and 22); the three others involved dosing of young adults to dichlorvos. The results of the BMD analyses for the acute studies revealed no evidence of age-related sensitivity. In the 7-day repeat-dose cholinesterase inhibition study, significant variation in the cholinesterase data precluded a meaningful determination of age-related sensitivity.

Non-guideline studies were available in the published literature that addressed male and female reproductive function as well as offspring behaviour. Rat offspring exposed to dichlorvos in utero, via lactation, and subsequently by gavage, exhibited behavioural deficits at dose levels that were comparable to maternal LOAELs from other reproductive studies. However, the results of these studies were confounded by the fact that offspring may have been dosed via gavage starting from six weeks of age. Thus, it is difficult to determine to what extent effects were attributable to in utero and lactational exposure, versus gavage exposure. In studies addressing male reproductive function in rodents, gavage administration of dichlorvos resulted in decrease in testicular weight, daily sperm production, number of spermatogenic cells, and sperm motility, as well as damaged seminiferous tubules and Sertoli cells, hypertrophy and changes in the number of Leydig cells, severe disturbances to spermatogenesis and an increased number of sperm with abnormal morphology. These studies did not result in the establishment of no observed adverse effect levels (NOAELs) for the aforementioned effects; however, the dose levels examined in these studies were higher than those expected to inhibit cholinesterase activity on the basis of the studies in the dichlorvos database. In a rat study addressing female reproductive function, gavage administration of dichlorvos resulted in a decrease in the number of estrus cycles, decreased durations of each phase of the estrus cycle (other than the diestrus phase) and significant alterations of the endometrium. These effects occurred just above the

NOAELs that were established in maternal animals in reproductive toxicity studies. Co-administration of vitamins C and E with dichlorvos did not result in complete protection to either the male or female reproductive effects that were induced by dichlorvos.

The genotoxicity of dichlorvos has been extensively assessed in older studies and foreign reviews as well as in recently published journal articles. Within the genotoxicity database, dichlorvos was mutagenic in numerous bacterial assays. Positive results were also observed in in vitro mammalian mutagenicity assays. These assays included DNA strand break, viral transformation and gene mutation assays. In vitro mammalian clastogenicity assays, including sister chromatid exchange and chromosomal aberrations, also produced positive results. An in vitro micronucleus assay demonstrated aneuploidy with dichlorvos exposure. An in vitro unscheduled DNA synthesis assay gave conflicting results. In summary, dichlorvos was considered an in vitro mutagen and clastogen.

In vivo mutagenicity and clastogenicity assays in mammals were generally negative, although positive results were obtained in some in vivo genotoxicity studies. These positive in vivo results were obtained in a sister chromatid exchange assay, a micronucleus test, a supplemental Comet assay for DNA damage as well as DNA damage and crossover recombination in Drosophila melanogaster. Another positive result was obtained in a supplemental in vivo micronucleus test in mouse keratinocytes when dichlorvos was dermally administered. In in vivo mammalian studies, dichlorvos produced some positive results, though the weight of evidence suggests that it is neither mutagenic nor clastogenic in vivo.

Published in vitro and in vivo literature studies investigated the potential of dichlorvos to induce low levels of DNA alkylation in mice and rats. Based on the results of these studies, it was determined that dichlorvos has a weak potential to induce low levels of DNA alkylation in rodents which could result in damage to DNA.

The potential carcinogenicity of dichlorvos has been extensively studied. Most studies have deficiencies and therefore were not used for the re-evaluation. This re-evaluation relied on the 2-year gavage NTP studies in both the rat and mouse while a non-NTP 2-year rat inhalation study was considered supplemental.

In a 2-year gavage study in the mouse, a dose-related increase in forestomach squamous cell carcinoma and/or papilloma was observed in males and females. Conclusions regarding the toxicological relevance of these carcinogenicity findings were difficult to reach for several reasons. Repeated bolus administration of dichlorvos would result in high sustained concentrations of dichlorvos in the mouse forestomach. Although humans have no organ similar to the forestomach, it is uncertain whether the rapid transit of dichlorvos through the human esophagus would result in sustained tissue levels prior to dichlorvos breakdown. The use of a corn oil vehicle may have impacted the toxicokinetics of dichlorvos as well as the lipid nutritional profile, thereby further confounding the results. A further limitation of this study was that only two dose groups were tested, thus making it difficult to identify true dose-response relationships.

Although arguments have been advanced that the irritating properties of dichlorvos may have contributed to the induction of these forestomach tumours, it is worth noting that no increases in other non-proliferative lesions (for instance erosions and thinning of gastric lining) were observed. The registrant suggested that dichlorvos had a similar mode of action (MOA) as butylated hydroxyanisole, a non-genotoxic promotor of forestomach tumours, which causes focal hyperplasia and induced replicative DNA synthesis. The MOA was unsubstantiated because no increase in focal hyperplasia of the stomach was observed in the dichlorvos mouse study. It is possible that the chronic effects of dichlorvos on mouse forestomach epithelium in the oral gavage bioassay were mediated via enhanced cell proliferation rather than by a genotoxic mechanism but the evidence for this was inconclusive.

The 2-year gavage study in the F344 rat suffered from limitations similar to those identified in the mouse study (that is, use of a corn oil vehicle and only two dose groups). Equivocal treatment-related findings in the study included increased incidences of alveolar/bronchiolar adenoma in males, mammary fibroadenoma, adenoma and carcinoma in females and leukemia (lymphocytic, monocytic, mononuclear or undifferentiated) in males. The incidence of pulmonary tumours in males was statistically significant for trend analysis but not statistically significant in pairwise comparison. The response for combined mammary tumours was also unclear as it lacked a classical dose-response pattern, was statistically significant in pair-wise analysis at the low-dose only and fell within the historical control incidence of the testing laboratory.

The observed mononuclear cell leukemia (MCL) incidence was statistically significant in trend and pairwise comparisons. However, the incidence of MCL fell within the historical control range of the testing laboratory and was less than the maximum incidence of the historical controls from the NTP. Additionally, dichlorvos did not alter the latency to MCL development. Furthermore, the higher incidence of MCL in treated groups did not result in higher mortality which generally would be expected since MCL is a rapidly progressive and uniformly fatal tumour. In an experimental MCL transplant study, dichlorvos was shown to accelerate the progress of MCL in MCL-inoculated animals; however, this study method has not been validated. Long-term studies in rats involving trichlorfon, which is metabolized to the biologically active metabolite dichlorvos, did not result in elevated incidences of MCL, though trichlorfon did increase the incidence of other tumour types at excessive doses (PRVD 2008-14, *Trichlorfon*).

An increased incidence of pancreatic exocrine tumours in male rats in the 2-year gavage study was the most robust carcinogenic response as it was statistically significant in trend and pairwise comparisons and exceeded the range of historical control data for the performing laboratory. Since corn oil has been shown to increase the rate of proliferative pancreatic lesions in male F344 rats, comparison to control data with corn oil vehicle was considered appropriate. However, even the control incidence for pancreatic tumours in males was high, exceeding the mean (but not the range) of the corn oil vehicle historical control data for both the testing laboratory and the NTP.

A dose-related increase in pancreatic exocrine tumours was also seen in females. Though this increase in females was not statistically significant, the incidence in the high-dose group exceeded the range of the corn oil vehicle historical control data for both the testing laboratory and the NTP.

A 2-year inhalation study with dichlorvos revealed no evidence of carcinogenicity in rats. This study had numerous limitations such as whole-body exposure, uncertainties regarding achieved dose (exposure from contamination of food, drinking water, dermal contact and grooming), the number of tissues examined was limited or not stated, low survival in male control animals and a lack of report details. Therefore, this study was considered to provide supplementary information for the re-evaluation of dichlorvos.

In summary, the PMRA concluded that the available evidence is insufficient to rule out the possibility that dichlorvos may be carcinogenic. Although available cancer studies have limitations, the risk assessment has an adequate margin to protect against these effects by ensuring that the level of exposure to humans is well below the lowest dose that resulted in tumours in test animals.

Results of the toxicology studies conducted on laboratory animals with dichlorvos, along with the toxicology endpoints for use in the human health risk assessment, are summarized in Appendix II, Tables 1 and 2.

Epidemiology

Numerous studies were identified which explored the potential health effects of dichlorvos exposure (among other pesticides) in human populations. The health outcomes examined included prostate cancer, lymphohematopoietic cancer (non-Hodgkin's lymphoma, multiple myeloma and leukemia), childhood cancer and diabetes. Studies reporting positive associations with dichlorvos exposure are detailed below. The results of the remaining studies did not identify any critical relationships between exposure to dichlorvos and adverse health outcomes; however, small numbers of exposed cases and/or limitations in study design preclude definitive conclusions.

Prostate Cancer

A nested case-control study was conducted in a predominantly Hispanic labour union in California to study the risk of developing prostate cancer (PMRA Number 2489919). Between 1987 and 1999, 222 newly diagnosed prostate cancer cases were identified for analysis. For each prostate cancer case identified, five age-matched controls, for a total of 1,110 controls, were randomly selected from the remainder of the cancer-free United Farm Workers union cohort. Exposure was measured from state records of pesticide usage in counties of employment. Information was collected on several demographic variables such as age, race, sex, residence, along with diagnostic variables (including stage at diagnosis, tumour size, histology and grade of tumour) and first course of treatment for all the cases. Data available from the files of the union that were used in the analysis included the types of crops and commodities that workers cultivated and the dates and location of employment. Hispanic farm workers with high levels of exposure to dichlorvos experienced an elevated risk of prostate cancer (OR = 1.35, 95% C.I. 0.93

- 1.96) compared to workers with lower levels of dichlorvos exposure. At the highest quartile of exposure for dichlorvos, the risk of developing prostate cancer increased (OR = 1.64, 95% C.I. 0.97 - 2.78) but this was not statistically significant.

The relationship between agricultural pesticides and prostate cancer incidence was examined in a prospective cohort study (Agricultural Health Study or AHS) of 55,332 male pesticide applicators from Iowa and North Carolina with no prior history of prostate cancer (PMRA Number 2533059). In Iowa, both commercial and farmer applicators were invited to participate in the study. In North Carolina, only private applicators were enrolled. Data were collected by means of self-administered questionnaires completed at the time of enrolment between 1993 and 1997. The enrolment questionnaire sought information on the use of 50 pesticides (ever/never), crops grown, livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, non-farm occupational exposures, smoking, alcohol consumption, fruit and vegetable intake, multiple vitamin use, medical conditions, medical conditions in first-degree relatives including a history of prostate cancer and basic demographic data. Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and the National Death Index to ascertain vital status. All applicators that had been diagnosed with prostate cancer prior to enrolment in this study were excluded from the analyses. The cancer incidence was then determined through population-based cancer registries from enrolment through to December 31, 1999. A total of 1,197 deaths occurred among male applicators during the mean follow-up period of 4.3 years. The study results indicated that exposure to dichlorvos resulted in an elevated risk (non-significant) of prostate cancer among subjects with a family history of prostate cancer (OR = 1.75, 95% C.I. 1.00 - 3.06) but not among those with no family history (OR = 0.95, 95% C.I. 0.66 - 1.37). The risk of developing any cancer other than prostate cancer among those exposed to each of the pesticides was examined and there was little evidence of an effect.

A follow-up study was conducted among pesticide applicators enrolled in the Agricultural Health Study (AHS) to examine the risk of developing prostate cancer following exposure to dichlorvos (PMRA Number 2489915). The cohort of pesticide applicators in North Carolina and Iowa that were recruited from December 1993 through December 1997 were followed through to December 31st, 2004. Study participants completed a comprehensive self-administered enrolment questionnaire which provided detailed exposure data, including information on the use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, basic demographics and lifestyle exposures, family history of cancer and information on 50 different pesticides including dichlorvos. Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and the National Death Index to ascertain vital status. Participants were asked how many years they applied dichlorvos, how many days it was used in an average year and in what decade they first used dichlorvos. Only first primary cancers were used in this analysis. Among the 49,762 licensed pesticide applicators eligible for analysis, 4,613 reported the use of dichlorvos. Dichlorvos exposure was classified as intensity-weighted cumulative exposure days (IWED) and these were categorized into tertiles based on the distribution among all cancer cases (less than 66, 66-589 and greater than 589 intensity-weighted dichlorvos exposure days). Those applicators who reported being exposed to dichlorvos and having no family history of prostate cancer showed a small reduced risk of prostate cancer (RR (rate ratio) = 0.96, 95% C.I. 0.77 - 1.21) while those with a family history of prostate cancer who reported using dichlorvos had a slightly increased risk (RR = 1.18, 95% C.I. 0.73-1.82), though both these were not significant. The RR increased to 1.42 (95% C.I. 0.75 - 2.70) in the highest exposure tertile of applicators with a family history of prostate cancer. Therefore, this study indicated that those pesticide applicators with no family history generally had negligible or slightly reduced risks of developing prostate cancer. The overall study results indicated that the incidence of all cancers combined was not associated with exposure to dichlorvos.

Lymphohematopoietic Cancers (Non-Hodgkin's Lymphoma, Leukemia and Multiple Myeloma)

During the 1980s, the National Cancer Institute (NCI) conducted three population based case-control studies of Non-Hodgkin's lymphoma (NHL) in the Midwestern United States, including the states of Nebraska, Kansas, Iowa and Minnesota (PMRA Number 2576215). Each of these studies focused on farming exposure to pesticides and data from the three studies have been pooled to examine pesticide exposures in farming activities as risk factors for the development of NHL in men. The large sample size (n=3,417) provided adequate numbers of exposed persons to analyse a set of pesticide exposures simultaneously, using hierarchical regression to adjust estimates based on prior distributions for the pesticide effects. The three case-control studies had slightly different methods of subject recruitment (described in detail below). Population-based controls were randomly selected from the same geographical areas as the cases, frequency-matched to cases by race, sex, age and vital status at the time of the interview. Interviews were conducted with the subjects or their next of kin if the subjects were dead or incapacitated. In each study, detailed questions were asked about the use of agricultural pesticides as well as other known or suspected risk factors for NHL. Following the exclusion of subjects who had missing data, 650 cases and 1933 controls were available for analysis. Each pesticide for which there were data from all three studies, and to which 20 or more persons were exposed, was included in the pooled analysis. Overall, the pooled results from these three studies indicated that the use of dichlorvos was not associated with an increased risk of developing NHL (OR = 0.9, 95% C.L. 0.4 - 2.0).

One of the population based case-control studies conducted by the National Cancer Institute examined the incidence of NHL in Eastern Nebraska (PMRA Number 2690526). The purpose of this study was to evaluate the role of the herbicide 2,4-dichloro-phenoxyacetic acid (2,4-D) in the development of NHL (not reported here) however other chemicals were also included. All cases of NHL diagnosed between July 1, 1983 and June 30, 1986 among white subjects 21 years of age and older and living in one of the 66 counties of eastern Nebraska were identified through the Nebraska Lymphoma Study Group and area hospitals. Telephone interviews were conducted with 201 NHL cases and 725 controls or with their next of kin, between May 1986 and October 1987. Control subjects were selected from residents of the same 66-county area by 3:1 frequency matching by race, sex, vital status and age (±2 years) to the combined age distribution of the cancer cases.

Analysis of organophosphate use, adjusted for use of 2,4-D showed an independent association with NHL (ever used: OR = 2.4, 1-5 days/year: OR = 1.7, 6-20 days/year: OR = 1.8, 21 or more days/year: OR = 3.1). However, the information gathered from this study was limited as no information was provided for dichlorvos; instead information was only available for the entire class of organophosphate pesticides.

A second population based case-control study was conducted by the NCI to examine the incidence of NHL in Iowa and Minnesota (PMRA Number 2574314). This case-control study utilized an in-person interview of 622 white men, 30 years of age or older, with newly diagnosed cases of NHL between 1980 and 1983 and 1,245 population-based controls in Iowa and Minnesota to measure the risk associated with farming and agricultural exposures. All newly diagnosed cases of NHL were ascertained from Iowa State Health Registry records and a special surveillance of Minnesota hospital and pathology laboratory records. In Iowa, the diagnosis period for eligibility was March 1981 to October 1983, and in Minnesota, October 1980 to September 1982. In Iowa, all cases who resided in the state were eligible. In Minnesota, eligibility was restricted to cases who resided in places other than the cities with little farming activity at the time of diagnosis. A population-based control group of white men without hematopoietic or lymphatic cancers was randomly selected and frequency-matched to NHL and leukemia cases by 5-year age group, vital status at time of interview and the state of residence. Interviews were conducted during the period of August 1981 to May 1984. Study results identified a non-significant elevated risk of developing NHL for men handling, mixing or applying dichlorvos. Associations were generally stronger for first use of dichlorvos prior to 1965 (OR = 1.8, 95% C.I. 0.8 - 3.9) than for those ever having handled dichlorvos (OR = 1.2, 95% C.I. 0.7 - 2.2).

A third population-based case-control study was conducted by the NCI to clarify whether agricultural use of insecticides affected the risk of developing soft-tissue sarcoma (STS), Hodgkin's disease (HD) and NHL in Kansas (PMRA Number 2690525). All newly diagnosed cases of STS, HD and NHL among white male Kansas residents, 21 years of age or older, from 1976 through to 1982, were identified through the University of Kansas Cancer Data Service, a population-based registry covering the state of Kansas. There were 200 men diagnosed with STS and 173 men with HD. A random sample of 200 men was drawn from the 297 men diagnosed with NHL from 1979 through 1981. The controls were white men from the general population of Kansas. Three controls (N=1005) were matched to each patient based on age (±2 years) and vital status. The patients and controls, or their next of kin, were interviewed by telephone between December 1982 and January 1984. Interviews were obtained from 133 patients with STS, 121 with HD, 170 with NHL and 948 controls, which represented 95% of the eligible subjects (patients 96%, controls, 94%). The results of this study demonstrated no association with increasing years of insecticide use but the risk of developing NHL increased significantly, but inconsistently with days of exposure per year. Other exposure variables, such as mixing and applying insecticides, application method and insecticide type, showed little or no association with NHL risk. No specific data were presented for the use of dichlorvos.

To determine whether the exposure to chemicals in an agricultural setting was related to an increased risk of developing leukemia, a population-based case-control interview study of leukemia and NHL (reported above) was conducted in Iowa and Minnesota (PMRA Number 2574315). All newly diagnosed cases of leukemia among white men 30 years of age or older were ascertained from tumour registry or hospital records both retrospectively (one year before the start of the study) and prospectively (two years after the start of the study). In Iowa, cases were ascertained from March 1981 to October 1983 through the Iowa Tumour Registry. In Minnesota, a special surveillance network including hospitals and pathology laboratories was created to identify all cases occurring between October 1980 and September 1982. Since the design of the study was to investigate potential agricultural hazards, cases residing in cities with little farming activity at the time of diagnosis were excluded from the study. Controls were selected from a population-based stratified sample of white men without lymphatic or hematopoietic cancer that were frequency-matched to the leukemia and NHL cases by 5-year age groupings, vital status at time of interview and the state of residence. During 1981-1984, in-person interviews lasting approximately 50 minutes were conducted with the subjects or with close relatives if the subjects were deceased or unable to be interviewed. A standardized questionnaire was used to obtain detailed information concerning residential history, drinking water sources, non-farm occupational history, smoking and alcohol use, use of unpasteurized dairy products, medical conditions, family history of cancer, and farm activities. Information concerning the use of 24 animal insecticides, 34 crop insecticides, 38 herbicides and 16 fungicides used on the farm was also obtained. This included the first and last year used and whether the subject personally mixed or applied the pesticide. In 1987, a supplemental interview of the Iowa subjects who participated in the initial interview was conducted to obtain information regarding the usual number of days per year that each previously reported pesticide had been handled. The final study population consisted of 578 (340 living, 238 deceased) cases and 1245 (820 living, 425 deceased) controls. The number of cases from Iowa (n = 293) and Minnesota (n = 285) were approximately equal. Odds ratios among farmers exposed to individual pesticides and families of pesticides were calculated for all incidences of leukemia and for all leukemia cell types, when there were sufficient numbers of exposed subjects. A significantly elevated risk of developing leukemia was observed following exposure to dichlorvos (OR = 2.0, 95% C.I. 1.2 - 3.5). The risk of developing leukemia for those subjects who had first handled dichlorvos at least 20 years prior to the interview was greater (OR = 2.4, 95% C.I. 1.1 - 5.4) than for all dichlorvos users. A significantly elevated risk by histological type was observed for chronic lymphocytic leukemia (OR = 2.2, 95% C.I. 1.0 - 4.6) and for chronic myelogenous leukemia (OR = 3.3, 95% C.I. 1.0 - 10.6) among those who ever handled dichlorvos. The risk of developing leukemia was greatest for subjects who handled dichlorvos for more than 10 days per year (OR = 3.8, 95% C.I. 1.0 - 14.8).

A case-control study was conducted to examine the association of multiple myeloma among white men living in an area of Iowa with a large agricultural industry (PMRA Number 2574312). Included in this study were all cases of multiple myeloma among white men 30 years of age or older diagnosed between 1981 and 1984 which were identified from the Iowa Health Registry. A standardized questionnaire was used to obtain detailed information on general farm activities and the use of pesticides including whether the subject personally mixed, handled or applied the pesticide, whether the subject usually used protective equipment when handling the pesticide and the first and last year the pesticide was used. Information on the frequency of pesticide use was not obtained. In-person interviews lasting approximately 50 minutes were conducted with subjects or with close relatives if subjects were deceased. Logistic models were used to calculate OR for multiple myeloma for individual pesticides that were handled personally by at least five cases. All OR were calculated using non-farmers as the referent group because they were not exposed to any farm-related activities. Vital status (alive, deceased) and age (less than 45, 45-64, 65 and older) were included in models to adjust for potential confounding. Other factors such as smoking and education were evaluated and found not to be confounders of agricultural risk factors. There were 173 white men with multiple myeloma and 650 controls available for this study. Results of this study revealed an elevated OR of 2.0 (95% C.I. 0.8 - 5.0, not statistically significant) for the risk of developing multiple myeloma in farmers who mixed, handled or applied dichlorvos. However, the failure to use protective equipment was not associated with a higher risk of developing multiple myeloma in farmers who mixed, handled or applied dichlorvos.

In a prospective cohort study (AHS) previously mentioned (PMRA Number 2489915), no elevation in the risk of developing lymphohematopoetic cancers was noted following exposure to dichlorvos (RR = 1.00, 95% C.I. 0.51 - 1.96).

Childhood Cancer

Through the AHS, a prospective study of certified pesticide applicators and their spouses in Iowa and North Carolina, the risk of childhood cancer (diagnosed from birth through 19 years of age) and the association of parental pesticide application was examined (PMRA Number 2489914). This study used a hybrid design, in which the prospective cohort of pesticide applicators and cancer cases among their children were both retrospectively and prospectively identified after parental enrolment. Persons applying for pesticide application licenses between 1993 and 1997 in North Carolina and Iowa were asked to participate in the study. The analyses were limited to private pesticide applicators (farmers) because information about children was collected only from the spouses of private applicators. At enrolment, pesticide applicators were asked to complete a questionnaire providing information on pesticide application practices and health-related behaviours. Spouses were enrolled through a questionnaire brought home by the licensed applicator, or by telephone. Females (applicators and spouses; n = 20,625) were also asked to complete a questionnaire on female and family health that collected information on children born during or after 1975. General questions included frequency of pesticide mixing and application (days/year), whether applicators personally mixed and applied pesticides (ever/never) and whether they personally mixed and applied pesticides more than 50% of the time when pesticides were used or required mixing (yes/no). Detailed exposure information (decade of first use, and frequency and duration of use) was solicited for 22 pesticides in the initial questionnaire and for 28 additional pesticides in the take-home questionnaire. Children for whom timing of use was missing were excluded from this analysis. Individual pesticides were treated as separate exposure variables in the analysis when there were five or more exposed cases. Individual pesticides were also grouped into classes (organophosphates, organochlorines, carbamates, chlorophenoxy compounds and pyrethroids) to create exposure variables based on potentially similar mechanisms of pesticide action. Applicators were also asked to indicate whether they generally used protective equipment, such as chemically resistant gloves, during pesticide application. A total of 21,375 children born during or after 1975 were enumerated by their mothers. Of these children, 17,357 (81%) resided in Iowa and 4,018 (19%) resided in North Carolina. Identifying information for children in Iowa was matched against the Iowa Cancer Registry to identify cases of childhood cancer arising between 1975 and 1998. Following exclusions, 17,280 children for whom the father was the primary licensed pesticide applicator were available for analysis.

Results of this study indicated that when dichlorvos was reported as being used by fathers prenatally, the OR (OR = 2.06, 95% C.I. 0.86 - 4.90) for the incidence of childhood cancer was increased. Since this result was based on small numbers (6 childhood cancer cases from 1,218 paternally exposed pesticide applicators; 7% of the total cohort) the significance of this finding is questionable.

Diabetes
In a prospective study of licensed pesticide applicators from Iowa and North Carolina, the potential relationship between lifetime exposure to specific agricultural pesticides and the incidence of diabetes was investigated (PMRA Number 2574316). In the AHS, 33,457 licensed applicators, predominantly non-Hispanic white males, were surveyed between 1993 and 1997. Study participants were then re-contacted between 1999 and 2003 for a follow-up telephone interview. The incidence of diabetes was self-reported with 1,176 diabetics and 30,611 non-diabetics available for analysis. The results of this study indicated that exposure to dichlorvos was associated with an increased risk of developing diabetes with ever having used dichlorvos (OR = 1.21, 95% C.I. 0.98 - 1.49) and cumulative days of dichlorvos use (for more than 100 days OR = 1.26, 95% C.I. 0.91 - 1.73).

Overall, the findings in the epidemiological studies were often limited by small numbers, self-reporting and/or the lack of reproducibility. The lack of reliable characterization of exposure was considered an important weakness in most studies. Of the positive associations noted, most showed a weak response. In conclusion, the available epidemiology data for dichlorvos did not further inform the current risk assessment.

The PMRA has concluded that although numerous human toxicity studies were available for dichlorvos, all clearly assessed systemic toxicity. Accordingly, these studies were not used by the PMRA in the re-evaluation of dichlorvos consistent with its current policy regarding use of human studies in risk assessment (SPN2016-01, *Restricted Use of Human Studies with Pesticides for Regulatory Purposes*). Most of these human studies were of limited quality; only one study (PMRA Numbers 1267324 and 1267325) was deemed sufficient for evaluation by the United States Environmental Protection Agency (USEPA) and the United States Human Studies Review Board (HSRB). Notwithstanding the policy implications regarding its use in risk assessment, this study also had some scientific limitations and provided little to further inform the risk assessment other than to confirm that the animal data are an appropriate surrogate for human information.

With respect to human poisoning incidents, dichlorvos has been implicated in numerous cases worldwide; however, relatively few of these cases were considered life-threatening or required hospitalization. Most common symptoms noted in humans following exposure to dichlorvos and dichlorvos-containing products included skin irritation and dizziness, followed by headache, diarrhea, epigastric pain, nausea, vomiting, shortness of breath, difficulty breathing, chest pain and loss of concentration. In some severe cases, delayed neurotoxicity, axonal degeneration and acute pulmonary edema, leg pain and paraesthesia were reported. In cases involving mortality, death was attributed to respiratory failure. Symptoms prior to death or in non-fatal cases consisted of excessive salivation, bronchial secretion, pulmonary edema, lacrimation, respiratory failure and coma (PMRA Numbers 2480292, 2506314 and 2534676).

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for dichlorvos. The database contains a 2-generation reproductive toxicity study in rats, oral developmental toxicity studies in mice (supplemental), rats and rabbits, as well as supplemental inhalation developmental toxicity studies in rats and rabbits. A series of developmental neurotoxicity studies and comparative cholinesterase inhibition studies in rats were also available. Overall, the database for dichlorvos was considered adequate for determining potential sensitivity of the young.

With respect to potential pre- and post-natal toxicity, no evidence of sensitivity of the young was noted in guideline studies. Slightly decreased mean pup weight and pup survival were noted in the offspring in the rat reproductive toxicity study at a dose level higher than that which resulted in inhibition of cholinesterase activity in parental animals. In rats, mice and rabbits, no evidence of teratogenicity or fetal sensitivity was noted in any of the developmental toxicity studies. Fetal effects, when present, were limited to reductions in body weight.

Rats were exposed to dichlorvos in a series of acute and repeat-dose cholinesterase inhibition studies. The results of benchmark dose analyses for the acute studies revealed no evidence of age-related sensitivity for young (PND 8, PND 15 and PND 22) and adult rats. In the 7-day repeat-dose cholinesterase inhibition study, no evidence of age-related sensitivity was noted in males or females for brain cholinesterase inhibition or in males for erythrocyte cholinesterase inhibition; significant variation with respect to erythrocyte cholinesterase inhibition in females precluded a determination of age-related sensitivity.

Overall, the available information did not demonstrate sensitivity of the young and as a result, the *Pest Control Products Act* factor has been reduced to 1-fold for dichlorvos.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to dichlorvos from potentially treated imported foods is also included in the assessment. Dietary exposure assessments are age-specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose. The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Sufficient information was available to adequately assess the dietary risk from exposure to dichlorvos. Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey, What We Eat in America (NHANES/ WWEIA) 2005-2010 available through the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS). Further details on the consumption data are available in Science Policy Note SPN 2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on dietary risk estimates and the residue chemistry information used in the dietary assessment, see Appendices III and IV.

3.2.1 Determination of Acute Reference Dose

General Population (including pregnant women, infants and children)
To estimate acute (single day) dietary risk for all populations, two co-critical acute cholinesterase inhibition studies in neonatal and young adult rats were selected. A $BMDL_{10}$ of 1.4 mg/kg bw was derived for brain cholinesterase inhibition in both studies. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied. The *Pest Control Products Act* factor was reduced to 1-fold as described above in the *Pest Control Products Act* Hazard Characterization Section; therefore, the composite assessment factor (CAF) for this exposure scenario is 100.

ARfD = 1.4 mg/kg bw / 100 = 0.014 mg/kg bw

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of residues of dichlorvos that would be likely on any one day, and using food and drinking water consumption and food and drinking water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure is not of concern.

Dichlorvos is also a metabolite and degradation product of naled, which is currently a registered pesticide. Since dichlorvos residues resulting from dichlorvos use cannot be distinguished from dichlorvos residues resulting from naled use, the assessment was conducted using residues of dichlorvos from all pesticide sources.

Also, because dichlorvos and naled have the same toxicological effects (that is, cholinesterase inhibition), a separate risk assessment was conducted that assessed the combined risk from exposure to both dichlorvos and naled.

Most of the residues of dichlorvos and naled were obtained from the Canadian Food Inspection Agency (CFIA) and the US Pesticide Data Program (PDP) monitoring programs and were generally non-detects. The few field trial or MRL residues of naled used in the assessment were expressed as dichlorvos equivalents. Dichlorvos residues in drinking water were obtained from modelling. Since current outdoor uses of dichlorvos are not expected to result in residues in drinking water, estimated environmental concentrations (EECs) of dichlorvos obtained from modelling of naled uses were used in the assessment. The full 50-year distribution of EECs from modelling was used in the probabilistic exposure calculation. In addition, the following inputs were used: available percent crop treated (PCT) information in Canada and in the US; 100% crop treated for all commodities for which no PCT information was available; available information on the proportion of domestic production and import supply; and available experimental processing factors. DEEM default processing factors were used when experimental processing factors were not available.

For dichlorvos, the acute dietary (food and drinking water) exposure estimates, at the 99.9^{th} percentile, were 3% of the ARfD for the general population and ranged from 2% to 5% of the ARfD for all population subgroups and are, therefore, not of concern. Acute dietary risks from combined exposure to both dichlorvos and naled are also not of concern.

3.2.3 Determination of Acceptable Daily Intake

General Population (including pregnant women, infants and children)

To estimate repeated dietary risk for all populations, the most suitable study was a 7-day repeat-dose oral cholinesterase inhibition study in neonatal and young adult rats. A $BMDL_{10}$ of 0.011 mg/kg bw/day was derived for brain cholinesterase inhibition in males from this study; data from both age groups were combined for BMD analysis due to the lack of statistically significant age-related differences. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied. The *Pest Control Products Act* factor was reduced to 1-fold, as discussed in the *Pest Control Products Act* Hazard Characterization Section above, resulting in a CAF of 100.

ADI = 0.011 mg/kg bw/day / 100 = 0.0001 mg/kg bw/day

This ADI provides a margin of 1,000 to the equivocal auditory startle response findings in PND 23 rats in the DNT study. This ADI also provides a margin of 10,000 to the mortalities noted in dams in the developmental toxicity study in rabbits by the inhalation route of exposure and 16,000 to the testicular effects noted in the non-guideline special oral reproductive toxicity study in male rats.

3.2.4 Cancer Assessment

The results of extensive investigations of the genotoxicity of dichlorvos indicate that it is an in vitro mutagen and clastogen. In in vivo mammalian studies, dichlorvos produced some positive results; however, the overall weight of evidence suggested that it is neither mutagenic nor clastogenic in vivo. The potential carcinogenicity of dichlorvos has been extensively studied; however, the available evidence is insufficient to rule out the possibility that dichlorvos may be carcinogenic. Although available cancer studies have limitations, there is a large margin (~40,000) between the proposed reference values for repeat-exposure and the lowest dose resulting in tumours in the available dichlorvos studies. In view of this, additional cancer studies are not required at this time, nor will an additional database factor be applied in the risk assessment.

3.2.5 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using the average consumption of different foods and drinking water and the average residue values on those foods and in drinking water. The estimated exposure was then compared to the ADI. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

For dichlorvos, the chronic dietary (food and drinking water) exposure estimate for the general population was 9% of the ADI. Chronic exposure estimates for population subgroups ranged from 7% to 24% of the ADI. Thus, chronic exposures to dichlorvos residues in food and drinking water do not pose risk concerns. Chronic dietary risks from combined exposure to both dichlorvos and naled are also not of concern.

3.3 Exposure from Drinking Water

Residues of dichlorvos in potential drinking water sources were estimated from water modelling.

3.3.1 Concentrations in Drinking Water

Dichlorvos residues in water sources may result from uses of both dichlorvos and naled. Dichlorvos is an environmental transformation product of naled. However, because dichlorvos is not registered for agricultural field use, the contamination of sources of drinking water resulting from dichlorvos applications would be negligible. Estimated environmental concentrations of dichlorvos resulting from dichlorvos applications were not modelled.

Estimated environmental concentrations of dichlorvos as a transformation product in potential drinking water sources from the use of naled were modelled at refined Level 1. The EECs in both surface water and groundwater were calculated using the Pesticide in Water Calculator (PWC) model with conservative inputs with respect to application rates and timing, and geographic scenarios. All scenarios were run using 50-year weather data. The model predicted that dichlorvos will not leach into groundwater sources (EEC = 0 ppm). Acute (90th percentile of yearly peak concentrations) and chronic (90th percentile of yearly average concentrations) EECs of dichlorvos resulting from run-off were predicted as 0.0018 ppm and 0.000014 ppm, respectively. These values are considered to be upper bound concentrations in surface water [please refer to the Environmental Assessment Section of this document for details]. For the acute exposure assessment, the full distribution of the 50-year yearly peak concentrations was used in the probabilistic exposure calculation model.

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with the acute 50-year EEC distribution and the chronic EEC point estimate incorporated directly in the dietary (food + drinking water) assessments. Please refer to Sections 3.2.2 and 3.2.4 for details.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate an MOE. This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

3.4.1 Toxicology Endpoint Selection for Residential and Occupational Exposure

Dermal Exposure

For short-, intermediate- and long-term dermal exposure, there were no suitable repeat-dose dermal toxicity studies upon which to base the risk assessment for dichlorvos. An 8-day dermal cholinesterase inhibition study in the guinea pig was considered supplemental due to the lack of details on the application method and the histopathological examination. A 117-day dermal cholinesterase inhibition study in the rat was also insufficient as animals were dosed only once every 72 hours and a 10-day dermal study in the monkey was outdated and did not establish a NOAEL. In the absence of a suitable dermal study, the 7-day repeat-dose oral cholinesterase inhibition study in neonatal and young adult rats was deemed appropriate for this endpoint. A $BMDL_{10}$ of 0.011 mg/kg bw/day was derived for brain cholinesterase inhibition in males from this study. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied resulting in a target MOE of 100. For residential scenarios the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization Section (please refer to Section 3.1.1 for details).

Inhalation Exposure
For short-, intermediate- and long-term inhalation exposure, there were no suitable repeat-dose inhalation toxicity studies upon which to base the risk assessment. Inhalation developmental toxicity studies in the rat and rabbit were considered supplemental based on numerous conduct and reporting deficiencies. A 90-day inhalation study in the monkey was only available as a draft document and was therefore considered supplemental. In the absence of a suitable inhalation study, the 7-day repeat-dose oral cholinesterase inhibition study in neonatal and young adult rats was deemed appropriate for these scenarios. A $BMDL_{10}$ of 0.011 mg/kg bw/day was derived for brain cholinesterase inhibition in males from this study. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied resulting in a target MOE of 100. For residential scenarios the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization Section (please refer to Section 3.1.1 for details).

Non-Dietary Incidental Oral Exposure
For short-term incidental oral exposure, the most suitable study was the 7-day repeat-dose oral cholinesterase inhibition study in neonatal and young adult rats. A $BMDL_{10}$ of 0.011 mg/kg bw/day was derived for brain cholinesterase inhibition in males in this study. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied resulting in a target MOE of 100. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization Section (please refer to Section 3.1.1 for details).

Dermal Absorption
A dermal absorption value of 30% was used for dichlorvos based on a chemical-specific in vivo dermal absorption study.

3.4.2 Non-Occupational Exposure and Risk Assessment

Non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

The following scenarios were assessed:

- Pest strips in homes and in commercial areas[3], such as, animal and farm buildings, milk rooms, motels, restaurants (non-food areas only), food processing plants (non-food areas only), industrial and commercial locations, kennels, garbage storage areas and containers.

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[3] Since commercial areas were specified on domestic-class labels, these uses were assessed as part of the residential scenario.

- Outdoor mosquito control
- Theaters and animal barns

Residential Applicator Exposure and Risk Assessment
A residential applicator refers to an individual (≥16 years old) who applies a domestic class product in or around the home. For dichlorvos, the only domestic class product available is the impregnated pest strip that may be used in garages, attics, crawl spaces, and sheds, occupied for less than 4 hours per day, or in areas that are continuously unoccupied for a minimum of 4 months. Residential applicator exposure from the use of pest strips in residential areas is expected to be minimal.

Residential Postapplication Exposure and Risk Assessment
Residential postapplication exposure occurs when an individual is exposed through dermal, inhalation and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment that has been previously treated with a pesticide. Pesticide treatment could be by a residential applicator using a domestic-class product, or a commercial applicator applying in residential areas.

While exposure may occur for people of all ages, adults (≥16 years old), youth (11<16 years old), and children (1<2 years old), were chosen as the index lifestages to assess, based on behavioural characteristics and the quality of the available data. Children 2 years old to < 11 years old are not assessed separately, for most scenarios, because their exposure is expected to be less than that of children 1 < 2 years old. Children (1<2 years) are expected to have a greater exposure because of additional routes of exposure (incidental oral) as well as a greater body surface area (cm^2) to body-weight (kg) ratio.

Postapplication residential exposure to dichlorvos is expected to be intermittent short-to-intermediate-term (up to 6 months) in duration, with the exception of indoor structural uses (that is, pest strips, theaters and animal barns) which is assumed to result in intermediate-to-long-term (1-12 months) exposure.

Pest Strips
Postapplication exposure is expected from the use of impregnated pest strips in areas of the home that are occupied up to 4 hours a day, as well as, the use of pest strips in animal and other farm buildings, milk rooms, motels, restaurants, food processing plants (non-food areas only), industrial and commercial locations, kennels, garbage storage areas, and containers that are occupied up to 4 hours per day. Pest strips may also be used in cottages, cabins and trailers, in areas that are to be continuously unoccupied for a minimum of 4 months following placement of the strips; postapplication exposure from this use is expected to be minimal.

Exposure estimates were based on a chemical-specific study submitted by the registrant (PMRA Number 2586571). The objective of the study was to measure dichlorvos concentrations following use of the pest strip in a treated space (closet) and the room adjacent to the closet under the extremes of high and low environmental conditions of air exchange rate, temperature, and humidity. The study also measured weight loss from the pest strip, and transferable residues from deposition onto surfaces. The study conditions did not capture the Canadian use scenario exactly in that the pest strip used in the study was smaller than the pest strip registered in Canada (16 g versus 65 g, respectively), and the pest strip was placed in a closet in the study whereas the pest strip is used in garages, attics and crawl spaces in Canada. Nonetheless, as this is the best available data, the study results were used for the risk assessment. Mean air concentration values were selected based on the time weighted average mean air concentration data measures in the adjacent room as well as the treated closet. The adjacent room data was selected to represent areas adjacent to rooms where the pest strip is placed (for example, bedroom above garage containing the pest strip). The closet data were selected to represent a scenario where the pest strip is placed in an open area, such as a garage or an attic, where individuals may be directly exposed.

It was assumed that exposure would be similar across use sites. Therefore, the postapplication exposure assessment is also considered to be representative of exposure to individuals present in commercial locations such as motels and restaurants.

Both inhalation and dermal exposures are possible; however, since the data (PMRA Number 2586571) indicated that the predominant route of exposure would be inhalation, a quantitative exposure assessment was conducted for the inhalation route only.

The calculated inhalation MOEs did not meet the target MOE for all age groups, and therefore, risks are of concern (see Appendix V, Table 1). The use of impregnated pest strips in inhabited homes, and in commercial locations, such as animal and other farm buildings, milk rooms, motels, restaurants, food-processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces, are proposed for cancellation. Since exposure from the use of pest strips in structures (for example, cottages, cabins and trailers) continuously unoccupied for at least 4 months following placement of the pest strips is considered to be minimal, risks are not of concern for this scenario.

Outdoor Mosquito Control in Residential Areas

Postapplication exposure estimates for individuals entering an area that had been previously treated with dichlorvos were generated using the USEPA SOPs (2012). The USEPA has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures when chemical- and/or site-specific field data are limited. The assumptions and algorithms may be used in the absence of, or as a supplement to, chemical- and/or site-specific data, and generally result in high-end estimates of exposure. The assumptions and algorithms relevant to the dichlorvos re-evaluation are outlined in the Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessments 2012, under "Section 5: Outdoor Fogging/Misting Systems".

Multiple applications were not assessed for outdoor aerosol space sprays and outdoor residential misting systems, since exposure on the day of application without any dissipation was assumed for the entire duration of exposure (for several months). This is considered to be a highly conservative assumption (that is, resulting in upper bound exposure estimates), when combined with the other exposure inputs in the Residential SOPs.

Both inhalation and dermal exposures are possible. The predominant route of exposure is expected to be inhalation due to the method of application and volatility of dichlorvos.

The calculated inhalation MOEs did not meet the target MOE for all age groups, and therefore, risks are of concern (see Appendix V, Table 2). Therefore, all mosquito control uses for dichlorvos in outdoor residential areas are proposed for cancellation. Although dermal exposures are also possible following use of dichlorvos for mosquito control, as there were risks of concern from the inhalation route, which is expected to be the predominant route, a quantitative dermal risk assessment was not conducted.

Theatres and Animal Barns

Postapplication exposure estimates for individuals entering theaters and animal barns commercially treated with dichlorvos were based on an air model developed by the USEPA using an exposure study from a food processing plant (USEPA, 1993). For further details on this study and assessment, see Postapplication Worker Exposure and Risk Assessment Section.

The predominant route of exposure is expected to be inhalation due to both the method of application and volatility of dichlorvos. Although dermal exposure is possible, since the results from the food processing study suggested that dermal exposure would be less than 3% of the total exposure (USEPA, 1993), and contact with potentially contaminated surfaces in theaters and animal barns would be expected to be minimal, a quantitative dermal risk assessment was not conducted.

The calculated inhalation MOEs met the target MOE for all age groups (see Appendix V, Table 3), when the required mitigation measures (that is, entry is not permitted until 4 days after application and after full ventilation has occurred) are considered. Therefore, risks are not of concern from the use of dichlorvos in theatres and animal barns.

3.4.3 Occupational Exposure and Risk Assessment

There is potential for exposure to dichlorvos in occupational scenarios from workers handling dichlorvos products during the application process and potential for postapplication exposure from workers entering into areas previously treated with dichlorvos.

Handler Exposure and Risk Assessment

For commercial-class products, there are potential exposures to mixers, loaders and applicators (M/L/As). The following scenarios were assessed:

- Mixing/loading of liquids for automatic application equipment in greenhouses producing cucumbers, tomatoes, and ornamentals; tobacco storage; dairies, piggeries, poultry houses, and barns; food processing plants, industrial plants, and warehouses; theaters; and for outdoor mosquito control.

- Mixing/loading and applying using handheld sprayers (mechanically pressurized handwand, backpack, manually pressurized handwand, and backpack) for greenhouse tomatoes and greenhouse cucumbers, greenhouse ornamentals, sheds, stables, barns, loafing sheds, pigpens, outdoor areas, poultry barns, outdoor living areas, picnic grounds, backyard areas, patios, latrines, loading docks, parking and refuse areas, and other areas around buildings.
- Mixing/loading and applying using truck mounted equipment for mosquito abatement (assessed using the Agricultural Handlers Exposure Task Force (AHETF) airblast data as a surrogate).
- Application of impregnated pest strips for use in insecticidal traps in outdoor areas.

Dichlorvos is used up to 2 times per week for as often as necessary. Therefore, exposure in indoor (that is, greenhouse or structural uses) and outdoor environments is expected to be intermittent long-term (≥6 months) and short-to-intermediate-term (<6 months) in duration, respectively.

The PMRA estimated handler exposure based on different levels of personal protective equipment (PPE):

- Mid-Level PPE: Cotton coveralls over long pants, long-sleeved shirt, and chemical resistant gloves.
- Max-Level PPE: Chemical resistant coveralls over long pants, long-sleeved shirt, and chemical-resistant gloves.
- Chemical Resistant Headgear. Chemical resistant headgear that covers the neck (for example, Sou'Wester hat, rain hat).
- Respirator: a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides

No appropriate chemical-specific handler exposure data were available for dichlorvos. Dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database Version 1.1 (PHED) and AHETF studies. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-specific exposure estimates based on formulation type, application equipment, mix/load systems and level of personal protective equipment. The open and closed cab airblast scenario (as surrogate data for ULV application for mosquito control), and open mix/load liquids scenario from AHETF were used in the risk assessment. In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing a respirator. This was estimated by incorporating a 90% protection factor for a respirator into the unit exposure values, where applicable. Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack applicator scenarios, which were based on moderate inhalation rates (27 L/min).

Dichlorvos is highly volatile (1.2×10^{-2} mm Hg); therefore, the use of inhalation values from PHED or AHETF are expected to underestimate inhalation exposure, while overestimating dermal exposures.

Calculated dermal and inhalation MOEs for M/L/As exceeded the target MOE only when automated application equipment, an extra layer of personal protective equipment (chemical-resistant coveralls), and in some cases, restrictions on the maximum amount handled per day (1.14 kg active ingredient per person) were considered. Uses where automatic application equipment is not agronomically feasible, are proposed for cancellation including for outdoor mosquito control or outdoor living areas, picnic grounds, backyard areas, patios, latrines, loading docks, parking and refuse areas, and other areas around buildings. Handler exposure from use of impregnated pest strips in outdoor areas was assumed to be minimal, and was not assessed quantitatively.

The results of the mixer/loader and applicator assessment are presented in Appendix VI, Table 1-3.

Postapplication Worker Exposure and Risk Assessment

Potential occupational dermal and inhalation postapplication scenarios include workers entering treated areas in the following sites:

- Greenhouses producing cucumbers, tomatoes, and ornamentals
- Structural sites (that is, tobacco storage, food processing plants, barns, industrial plants, theaters, and warehouses)
- Outdoor pest strips in insecticidal traps in agricultural areas

Postapplication exposure was assumed to be intermittent long-term (>6 months) in duration for greenhouses and structural sites, and intermittent short-to-intermediate term in duration for outdoor pest strips in agricultural areas. Due to the high vapour pressure of dichlorvos, inhalation exposure is expected. The degree of dermal exposure would be dependent on the deposition of dichlorvos following spray application, the rate of volatilization, dissipation of dislodgeable residues and potential worker activities involving contact with treated surfaces.

Greenhouses Producing Cucumbers, Tomatoes, and Ornamentals

Potential exposure to postapplication workers was estimated using updated activity-specific transfer coefficients (TCs), and chemical-specific dislodgeable foliar residue (DFR) and air monitoring data. The DFR refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. The TC is a measure of the relationship between exposure and DFRs for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies. The TCs are specific to a given crop and activity combination (for example, harvesting cut flowers) and reflect standard agricultural work clothing worn by adult workers. Activity-specific TCs from the Agricultural Re-Entry Task Force (ARTF) were used. Postapplication exposure activities for agricultural crops include (but are not limited to): harvesting, pruning and scouting. For more information about estimating worker postapplication exposure, refer to the PMRA's regulatory proposal PRO2014-02, *Updated Agricultural Transfer Coefficients for Assessing Occupational Post-Application Exposure to Pesticides.*

A chemical-specific study in greenhouses that measured dichlorvos DFR and air concentrations was used to assess postapplication dermal and inhalation exposure from activities in greenhouses producing cucumbers, tomatoes, and ornamentals (Manninen et al., 1996). In this study, exposure to greenhouse workers was examined following application of dichlorvos using an automatic cold fog generator. Dichlorvos was applied to two greenhouses containing roses at a rate of 8.3 to 50 mg/m^3.

For workers entering a treated site, restricted-entry intervals (REIs) are calculated to determine the minimum length of time required before workers can safely enter after application to perform tasks involving hand labour. An REI is the duration of time that must elapse in order for air concentrations and residues to decline to a level at which there are no risks of concern for postapplication worker activities (for example, in the case of dichlorvos, performance of a specific activity that results in exposures above the target MOE of 100).

Calculated combined (that is, inhalation and dermal) MOEs for agricultural worker postapplication exposure to dichlorvos in greenhouses exceeded target MOEs with REIs ranging from 4 to 20 days. As REIs greater than 4 days are considered to be agronomically unfeasible, use of dichlorvos in greenhouses producing cucumbers, tomatoes, and cut flower ornamentals is proposed for cancellation. For potted greenhouse ornamentals (non-cut flowers), target MOEs were reached on Day 4; therefore, risks are not of concern with a 4-day REI. The greenhouse postapplication exposure risk assessment is summarized in Appendix VI, Table 1.

Structural Sites (Tobacco Storage, Food Processing Plants, Barns, Industrial Plants, Theaters, and Warehouses)

Postapplication exposure estimates for individuals entering theaters and animal barns commercially treated with dichlorvos were based on an air model developed by the USEPA. The decay constant and initial air concentration used in the model were based on a chemical-specific food processing plant study (USEPA, 1993) described in the USEPA Revised Preliminary HED Risk Assessment for Dichlorvos (August, 2000) and a revision document (June, 2000). In the study, dichlorvos was applied at a rate of 25.8 mg a.i./m^3 by multiple wall-mounted fogging unit and, in one area, a portable electric fogger.

The predominant route of exposure is expected to be inhalation due to the method of application and volatility of dichlorvos. Although dermal exposure is possible, since the results from the food processing study suggested that dermal exposure would be less than 3% of the total exposure (USEPA, 1993), and contact with potentially contaminated surfaces in structural sites is expected to be minimal, a quantitative dermal risk assessment was not conducted.

Calculated inhalation MOEs exceeds the target MOE with a restricted-entry interval (REI) of 4 days and following ventilation. Therefore, risks are not of concern from the use of dichlorvos in structural sites provided that worker entry occurs 4 days after application and full ventilation has occurred (Appendix VI, Table 2).

Outdoor Pest Strips in Agricultural Areas

Postapplication exposure following use of outdoor pest strips in insecticidal traps is expected to be minimal since the traps are usually placed in isolated areas and any dichlorvos released into the outdoor air would be expected to quickly dissipate. Therefore, the use of dichlorvos-impregnated pest strips in outdoor insecticidal traps in agricultural areas is not of concern.

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

In the absence of suitable inhalation and dermal toxicity studies, a 7-day repeat-dose oral cholinesterase inhibition study in neonatal and young adult rats was considered appropriate for the oral, dermal and inhalation components of the short-, intermediate and long-term aggregate risk assessment. A BMDL_{10} of 0.011 mg/kg bw/day was derived for brain cholinesterase inhibition in males from this study. Standard uncertainty factors of 10-fold for intraspecies variability and 10-fold for interspecies extrapolation were applied resulting in a target MOE of 100. For residential scenarios the *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization Section.

3.5.2 Residential, Non-Occupational and Dietary Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures. Additionally, only exposures from routes that share common toxicological points of departure are aggregated.

An aggregate risk assessment was conducted for individuals entering commercially treated theaters and animal barns. As there were risks of concern associated with use of pest strips in inhabited areas and outdoor mosquito control, these uses are proposed for cancellation, and thus, an aggregate assessment was not conducted for these uses. In addition, as minimal exposure would be expected from the use of pest strips in areas that are continuously unoccupied for at least 4 months after pest strip placement, such as cottages, cabins, and trailers, an aggregate risk assessment was not conducted for this use.

The calculated aggregate MOEs met the target MOE for all age groups (see Appendix VIII, Table 1) when the mitigation measures required to protect postapplication workers in structural sites (that is, a 4-day REI) were taken into consideration (see Postapplication Worker Exposure and Risk Assessment Section). Therefore, risks are not of concern from use of dichlorvos in theaters and animal barns.

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Dichlorvos belongs to a group of chemicals classified as organophosphates. Organophosphates have a common mechanism of toxicity wherein they all process the ability to interact with the cholinesterase enzyme ultimately leading to neurotoxicity. A cumulative assessment will be undertaken upon completion of the re-evaluation of the individual chemicals in the organophosphate group with all relevant chemicals and scenarios of the common mechanism group.

3.7 Incident Reports

As of 12 June 2017, 19 human incident reports involving dichlorvos have been submitted to the PMRA. Eighteen of these human incident reports involved dichlorvos-impregnated pest strips used to control flies and mosquitos in homes and farms. The strip is hung in an enclosed space and is effective for up to four months.

All incidents were minor or moderate in severity. The incidents related mostly to the location and/or way in which the product was applied, and misuse of the product was frequently reported. More than half of the people affected were exposed to areas in which the pest strip was situated. Similar trends were observed in the US, in which the use of pest strips in homes that were occupied for more than 4 hours a day (a misuse) was the most frequently reported type of exposure.

Based on the incident data, the primary panel on dichlorvos-impregnated indoor pest strip products must be modified to more clearly indicate allowed areas of use.

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

A summary of physical and chemical properties and environmental fata data for dichlorvos in the terrestrial and aquatic environments can be found in Appendix IX, Tables 1 to 4.

Dichlorvos enters the environment when used as an insecticidal fog or surface spray outdoors on small, localized areas, to control various insect pests. The physico-chemical properties of dichlorvos indicate that it is readily soluble in water. Dichlorvos has intermediate to high volatility from dry surfaces. Based on Henry's law constant, however, it is only slightly volatile from moist soil or water surfaces (Appendix IX, Table 1). Some evidence has indicated that dichlorvos volatilizes rapidly (within a few hours) from leaf surfaces, such as when applied as a surface spray on vegetation. When used as a fogging application, the fine droplets of dichlorvos are expected to remain suspended in air for a period of time and are likely to evaporate while suspended. Once in air, dichlorvos is expected to degrade rapidly as it is susceptible to photochemical oxidative reactions, having a half-life estimated to be <0.5 to 2 days. Based on this, long-range transport is not expected.

In the terrestrial environment, hydrolysis is an important route of transformation under environmentally-relevant pHs (pH 5 to 9) and temperatures (15-25°C), where half-lives are in the range of 0.88 to 30 days. Direct phototransformation is not expected to be an important route of abiotic transformation in soil. Laboratory aerobic biotransformation studies conducted on a wide range of soils resulted in DT_{50}s for dichlorvos ranging from 1 hour to 19.3 days, which would classify it as non-persistent to slightly persistent. A high level of transformation occurred rapidly, with the production of transient, intermediate transformation products including desmethyldichlorvos, 2,2-dichloroacetaldehyde, and dichloroethanol. Studies indicated high CO_2 capture in non-sterile soils and very little capture in sterile treatments. Dichlorvos transformed under anaerobic soil conditions with a DT_{50} of 6.3 days in sandy loam soil, which would classify it as non-persistent. The major transformation products were 2,2-dichloroacetic acid (DCA), 2,2-dichloroacetaldehyde, and 2,2-dichloroethanol. Therefore, in addition to hydrolysis, biotransformation is an important route of transformation of dichlorvos in soil and, overall, dichlorvos is not expected to persist in soil.

Dichlorvos is predicted to have high (K_{oc} 50-150) to very high (K_{oc} 0-50) mobility in soil based on K_{oc} values alone. Consideration of the criteria by Cohen[4] and the Gustafson equation indicates that dichlorvos may leach. However, laboratory studies of column leaching indicated that no dichlorvos was found in leachate, and it was likely that extensive transformation (hydrolysis and microbial transformation) of dichlorvos occurred during leaching and prior to measurement. Results from field studies varied. One finding indicated that up to 20% of dichlorvos applied to soil penetrated to a depth of 30 cm within 5 days of application while other field studies indicated that dichlorvos was not detectable at any soil level. The transformation product DCA was detected in the 0 to approximately 10 cm soil layer further indicating that degradation of dichlorvos is likely occurring in the upper soil layers. Based on the available evidence, dichlorvos may be mobile in soil under certain conditions but it is unlikely to leach significantly and reach groundwater or persist because of its rapid rate of degradation through hydrolysis and microbial activity in the soil column.

The UV-absorption spectrum indicates that direct photolysis of dichlorvos should not occur under normal environmental conditions at the earth's surface. There is some evidence, however, that indirect photolysis may occur in the presence of sensitizers in water.

Aquatic biotransformation studies in water/sediment systems indicated that transformation of dichlorvos (whole system DT_{50} <1 d) was rapid and that it would be classified as non-persistent. Similar intermediate transformation products were identified to those found in soil studies and a high degree of mineralization occurred rapidly. Aerobic biotransformation is, therefore, an important route of transformation of dichlorvos in aquatic systems. No data were available to determine the anaerobic aquatic biotransformation of dichlorvos.

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[4] Cohen, S.Z., S.M. Creeger, R.F. Carsel and C.G. Enfield. 1984. Potential for pesticide contamination of groundwater resulting from agricultural uses. Pages 297-325 In R.F. Krugger and J.N. Seiber, eds., Treatment and Disposal of Pesticide Wastes. ACS Symposium Series No. 259. American Chemical Society, Washington, DC, pp. 297-325.

Dichlorvos has a log K_{ow} of 1.47 at 20°C, which would indicate that it has a low potential for bioaccumulation. In a bioaccumulation study with fish, low concentrations of dichlorvos in tissues decreased rapidly during the depuration phase and were below the limit of detection within 6 hours. Thus, dichlorvos is not expected to bioaccumulate in fish exposed to residues in water.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated EECs are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (that is, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

Minimal exposure to the environment is expected through uses of dichlorvos such as pest strips, application on livestock, stored food and feed, and when used indoors. Therefore, EECs were not calculated for these uses and a risk assessment was not conducted. Exposure to non-target organisms as a result of uses for greenhouse food and non-food crops and other outdoor sites (for example, fogging and space spray for human habitat and recreational areas) cannot be quantified but was considered where relevant. Risk to non-target organisms from these uses was, therefore, assessed qualitatively.

Fogging for mosquitoes requires that dichlorvos be dispersed into the air as very small droplets, to allow the pesticide to remain suspended for longer periods of time to contact the target. Ultra-low volume applications are only conducted under environmental conditions that ensure optimal product movement. Droplets containing dichlorvos are, therefore, not expected to deposit in significant amounts in the environment and any residues of dichlorvos will breakdown or dissipate quickly. Therefore, the amount of spray that deposits on soil and water is expected to be minimal, and persistence in these media is low. Some residues may deposit on vegetation; however, it is expected that dichlorvos will dissipate rapidly from plant surfaces through volatilization and other degradation pathways under most environmental conditions. Fine droplets are expected to evaporate while suspended in the air and dichlorvos will be degraded by atmospheric photochemical reactions. In addition, fogging programs will be conducted in the early morning and late evening, which will further minimize the potential for exposure of non-target organisms.

Surface spray applications are relatively small, localised treatments, using hand-held equipment, over areas such as outdoor living areas, picnic grounds, backyard areas, patios, latrines, loading docks, parking areas, refuse areas and other areas around buildings. Spray drift is minimal when using such equipment and interception of the spray by the vegetation will reduce the amount reaching soil. Runoff is not expected to be a significant source of entry to aquatic systems because treated areas are targeted and relatively small, and dichlorvos breaks down quickly in soil and water. Volatilisation from plants and inert surfaces, followed by subsequent breakdown in air, is also expected to occur rapidly, and will minimise any residues left after treatment.

Effluent from greenhouses may be a route of exposure of dichlorvos to aquatic systems. Exposure to terrestrial systems is not expected from this use. A qualitative assessment of this use was conducted for aquatic organisms.

4.2.1 Risks to Terrestrial Organisms

Earthworms
The 14-d LC_{50} of dichlorvos to the earthworm *Eisenia fetida* (aka *Eisenia foetida foetida)* ranged from 14 to 80.9 mg/kg dry soil, with a no observed effect concentration (NOEC) stated to be < 12.3 mg/kg. Fogging, surface spray, and applications in greenhouses are not expected to result in significant residues of dichlorvos in soil. Therefore, risk to earthworms from these uses is considered to be negligible.

Bees and other non-target arthropod species
Laboratory tests show that dichlorvos is highly toxic to honey bees (*Apis mellifera*), via topical application or oral dosing resulting in LD_{50} values ranging from 0.052 µg per bee to approximately 0.9 µg per bee. Although no toxicity studies were available for other non-target arthropod species, effects are expected as dichlorvos is an insecticide. If bees and other non-target arthropods are present at the time of treatment or are foraging on flowers shortly after a surface spray has occurred, effects are expected. However, mosquito fogging programs are conducted in the evening, at night or early morning, when honeybees and other beneficial insects are less likely to be active. It is expected that populations will not be affected and any losses will

be mitigated by recolonization of insects from untreated areas. Similarly, potential impacts to bees due to exposure through surface spray and fogging applications can be mitigated by avoiding application of dichlorvos around blooming plants. This will also reduce potential for exposure of other beneficial insects.

Therefore, statements are required on the label to advise users that exposure to bees may be harmful, and application should occur during times of minimal foraging and to avoid application around blooming plants. Precautionary label statements for greenhouse uses will also be required to inform users of the potential for toxicity to insects used for pollination and biocontrol.

Birds and mammals
The information available on the toxicity of dichlorvos to birds and mammals is summarized in Appendix IX, Table 5. The potential exposure of birds and mammals to dichlorvos is primarily through the ingestion of food items that have received spray from the product either from fogging or a direct spray; spray drift from hand-held application equipment is not expected to be significant.

As a surface spray, dichlorvos is applied to small, localised areas in and around human habitation and recreational areas which may include vegetation used as food sources by birds and wild mammals. It is not expected that birds and mammals will be grazing recently treated areas extensively or as a sole source of food. In addition, dichlorvos transforms rapidly in the environment; under certain conditions, this may occur within a few hours to a few days (see Appendix IX, Table 2). Therefore, the likelihood that an animal would consume enough food contaminated with dichlorvos to cause an acute or reproductive effect is limited and risks of concern to birds and wild mammals are not expected. However, due to the inherent toxicity of dichlorvos to birds and mammals, label statements informing users of the toxicity to birds and mammals will be required.

For the fogging use, if any dichlorvos deposits on vegetation or other food items for birds and mammals, it is expected to dissipate rapidly. In addition, fogging occurs at times when many non-target organisms are less active. As a result, risks of concern to birds and mammals are not expected. Precautionary label statements will, however, be required to inform the user of the inherent toxicity of dichlorvos to birds and mammals.

Plants
No studies were available addressing the toxicity of dichlorvos to vascular plants. Risk to plants is not expected to be a concern due to the insecticidal mode of action of dichlorvos and long history of use on plants. In addition, direct spray applications are small and localized, and no incident reports involving effects of dichlorvos on plants have been submitted to the PMRA.

4.2.2 Risks to Aquatic Organisms

Dichlorvos can be very highly toxic to freshwater and marine fish and invertebrates (Appendix IX, Tables 6 to 10). Information regarding the toxicity of dichlorvos to algae and aquatic vascular plants was not available, although risk to plants is not expected due to the insecticidal mode of action of dichlorvos. As exposure to aquatic environments through spray drift and runoff is expected to be minimal due to the methods of application (fogging with small droplets or hand-held equipment for outdoor surfaces) and small areas receiving direct application as a surface spray, no risks of concern to aquatic organisms were identified from these uses.

A qualitative assessment was conducted to assess the effects to aquatic organisms potentially exposed to discharge of greenhouse process water that may contain residues of dichlorvos and its transformation products. Estimating levels of residues in effluent under this use pattern is difficult, as water used in greenhouses is reused throughout day to day processes prior to discharge at a later time. In addition, there are multiple applications at different times throughout the crop production process, and for different crops. Based on laboratory studies, however, dichlorvos is highly toxic to fish and very highly toxic to aquatic invertebrates. Therefore, it is important to mitigate potential release of effluent containing residues of dichlorvos to aquatic systems through this use. Precautionary label statements will be required to inform users of the toxicity to aquatic organisms. In addition, a label statement will be required stating that effluent containing this active ingredient, from use of dichlorvos in greenhouses, should not be discharged into waterbodies.

4.2.3 Environmental Incident Reports

Environmental incident reports are obtained from two main sources; the Canadian pesticide incident reporting system (including both mandatory reporting from the registrant and voluntary reporting from the public and other government departments) and the USEPA Ecological Incident Information System (EIIS).

As of 12 June 2017, there were no environmental incident reports involving dichlorvos submitted to the PMRA. The USEPA's EIIS was queried for dichlorvos incidents that were available in the database as of 5 October 2015; there were six cases. According to a previous USEPA assessment, the incidents were associated with exposure through ingestion of treated feed (mallard duck), exposure due to industrial operations (unspecified organisms), unspecified exposure to birds causing mortality (bluebirds), exposure from secondary poisoning (red-tailed hawk), exposure due to drift from an unincorporated broadcast application (fox), and unspecified exposure to bees in China (honeybees). Where it was possible to determine a means of exposure for reported incidents (ingestion of treated feed, industrial operations, secondary poisoning, and drift from a broadcast application), the Canadian use patterns would not fall within these methods based on the information provided. For the incidents associated with an unspecified means of exposure, it is unknown if these would have been a result of use patterns similar to those in Canada.

5.0 Value Assessment

Dichlorvos is registered for the management of aphids and whiteflies in greenhouse cucumbers, greenhouse tomatoes and greenhouse ornamentals, to help maintain high quality, greenhouse grown plants with good visual appeal. Aphids can be serious and persistent pests in the greenhouse due to the high growth rate of their populations. Whiteflies are a major pest of greenhouse crops, including tomatoes and cucumbers, as well as many ornamental species. The presence of these insect pests, shed skins, and honeydew, as well as the reduction of plant vigour, can impact the quality, grading and value of a wide range of greenhouse crops. The low persistence of dichlorvos makes it highly suitable for end-of-season pest clean-up operations. This is necessary before the introduction of biological controls, such as beneficial insects to manage aphid and whitefly populations during the production cycles.

Every year raw tobacco and manufactured tobacco products are lost to two major storage pests, the cigarette beetle, *Lasioderma serricorne* (F) and the tobacco moth, *Ephestia elutella* (Hübner). Postharvest management of both insects is essential for maintaining the quality of stored tobacco for producers. User groups have indicated that while there are alternative products registered for these insects, such as pyrethrins, they are not as effective as dichlorvos.

Insect traps are placed in orchards and fruit or vegetable farms to positively identify insect pests and assess population levels, to determine which pest control methods are best deployed. Dichlorvos is effective when used in conjunction with these insect traps to monitor insect pest populations in fruit and vegetable crops. The pheromone attracts the insects while the vapour action and rapid knockdown effect of dichlorvos kills the insects.

The domestic product is an insecticide strip used in structures including homes and livestock barns to control flies, mosquitoes and other small flying insects. Insecticide strips containing dichlorvos are easy to use and provide pest control for up to 4 months.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

In accordance with the PMRA Regulatory Directive DIR99-03,[5] the assessment of dichlorvos and its transformation products against Track 1 criteria of Toxic Substances Management Policy (TSMP) under *Canadian Environmental Protection Act* was conducted. It determined that:

- Dichlorvos does not meet all Track 1 criteria, and is not considered a Track 1 substance (refer to Appendix IX, Table 11)
- Dichlorvos does not form any transformation products that meet all Track 1 criteria.

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical grade active ingredient and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[8] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

> Technical grade dichlorvos and associated end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through the PMRA formulant initiatives and Regulatory Directive DIR2006-02. For some products containing dichlorvos, aromatic petroleum distillates are present as formulants. A quantitative risk analysis on non-target aquatic organisms was not conducted for these formulants as exposure is expected to be limited based on the registered use patterns. A standard label statement will be required indicating that the product contains aromatic petroleum distillates and that these substances are toxic to aquatic organisms.

7.0 Conclusion

With respect to human health, risks of concern were identified for some residential and occupational exposures to dichlorvos. Therefore, cancellation of uses for greenhouse cucumbers and tomatoes, greenhouse cut flower ornamentals, outdoor mosquito control, outdoor residential living areas, and indoor pest strips (excluding areas that are unoccupied for a minimum of 4 months), is proposed. Mitigation measures are required for all remaining uses. Exposure from the remaining uses is unlikely to affect human health when used according to the proposed label directions.

Dichlorvos enters the environment when used to control insects in and around human habitation and other outdoor living spaces, or when it is present in water discharges from use in greenhouses and mushroom houses. When used according to the proposed label directions, dichlorvos is not expected to pose risks of concern to the environment.

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[6] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[7] NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.*

[8] DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

Dichlorvos provides consistent and effective control of a range of economically important insect pests on greenhouse crops and indoor and outdoor structural sites. The low persistence of dichlorvos makes it a very useful tool in greenhouse tomato, cucumber and ornamental integrated pest management (IPM) programs, where it is effective for end-of-season control of insect pests between crop cycles before the introduction of beneficial insects.

List of Abbreviations

♂	males
♀	females
↑	increased
↓	decreased
µCi	microcurie
µg	microgram
µM	micromolar
µmol	micromole
AChE	acetyl cholinesterase
ACP	acid phosphatase
ADI	acceptable daily intake
ADP	adenosine diphosphate
AHETF	Agricultural Handlers Exposure Task Force
AHS	Agricultural Health Study
a.i.	active ingredient
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Re-Entry Task Force
AST	aspartate aminotransferase
atm	atmosphere
ATPD	area treated per day
BAF	bioaccumulation factor
BCF	bioconcentration factor
BChE	brain cholinesterase
BHA	butylated hydroxyanisole
BMD	benchmark dose
BMDL	benchmark dose lower confidence limits
BuChE	butyrylcholinesterase
bw	bodyweight
bwg	bodyweight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CDC	Centers for Disease Control and Prevention
CEPA	Canadian Environmental Protection Act
CFIA	Canadian Food Inspection Agency
ChE	cholinesterase
CHO	Chinese hamster ovary
C_i	initial air concentration
cm	centimetres
CO_2	carbon dioxide
C_o	predicted air concentration
CPK	creatine phosphokinase
d	day(s)

DCA	2,2-dichloroacetic acid
DEEM	Dietary Exposure Evaluation Model
DEEM-FCID	Dietary Exposure Evaluation Model-Food Commodity Intake Database
DFR	dislodgeable foliar residue
DMP	dimethyl phosphate
DNA	deoxyribonucleic acid
DNT	developmental neurotoxicity
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
EC_{50}	effective concentration on 50% of the population
ECC	estimated environmental concentration
ECG	electrocardiogram
EChE	erythrocyte cholinesterase
EEG	electroencephalogram
EIIS	Ecological Incident Information System
EPA	Environmental Protection Agency
EPL	Experimental Pathology Laboratories, Inc.
e-PRS	PMRA's Electronic Pesticide Regulatory System database
F_0	parental generation
F1	first generation
fc	food consumption
fe	food efficiency
FIR	food ingestion rate
FOB	functional observational battery
FSH	follicle stimulating hormone
g	gram(s)
GD	gestation day
GGT	gamma-glutamyl transferase
GI	gastrointestinal
ha	hectare(s)
HD	Hodgkin's disease
HDT	highest dose tested
Hct	hematocrit
HCl	hydrogen chloride
Hg	mercury
Hgb	hemoglobin
hr(s)	hour(s)
5-HT	5-hydroxytryptan
i.p.	intraperitoneal
IPM	integrated pest management
IR	inhalation rate
IUPAC	International Union of Pure and Applied Chemistry
IWED	intensity-weighted cumulative exposure days
K_F	Freundlich adsorption coefficient
K_d	soil-water partition coefficient
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient

K_{om}	adsorption quotient normalized to organic matter
K_{ow}	octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD	lactation day
LD_{50}	lethal dose to 50%
LDH	lactate dehydrogenase
LDL	low density lipoprotein
LH	Luteinizing hormone
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	lowest observed effect concentration
m	metre(s)
MCH	mean corpuscular hemoglobin
MCL	mononuclear cell leukemia
MCV	mean corpuscular volume
mg	milligram(s)
min(s)	minute(s)
mL	milliliter(s)
M/L/A	mixer/loader/applicator
mm	millimetre(s)
MMP	monomethyl phosphate
MNNG	1-methyl-3-nitro-1-nitrosoguanidine
MOA	mode of action
MOE	margin of exposure
mPa	milliPascal
MPHG	mechanically pressurized hand-gun
MPHW	manually pressurized handwand
mol	mole
MRL	maximum residue limit
N/A	not applicable
NADP	nicotinamide adenine dinucleotide phosphate
NCHS	National Center for Health Sciences
nCi	nanocurie
NCI	National Cancer Institute
ng	nanogram
NHANES/WWEIA	National Health and Nutrition Examination Survey, What We Eat in America
NHL	Non-Hodgkin's lymphoma
NIOSH	National Institute for Occupational Safety and Health
nm	nanometre
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
N/S	not stated
NTE	neuropathy target esterase
NTP	National Toxicology Program
OC	organic carbon content

OECD	Organisation for Economic Co-operation Development
OM	organic matter content
OPIDN	organophosphate-induced delayed neuropathy
OR	odds ratio
PChE	plasma cholinesterase
PCT	percent crop treated
PDP	US Pesticide Data Program
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PND	postnatal day
PPE	personal protective equipment
ppm	parts per million
PWC	pesticide in water calculator
RBC	red blood cells
RD	residue definition
RDS	replicative DNA synthesis
REI	restricted-entry interval
RER	rough endoplasmic reticulum
RfD	reference dose
RNA	ribonucleic acid
RQ	risk quotient
RR	rate ratio
SER	smooth endoplasmic reticulum
SOP	standard operating procedure
STS	soft tissue sarcoma
T½	half-life
TC	transfer coefficient
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
TWA	time-weighted average
UDS	unscheduled DNA synthesis
ULV	ultra-low volume
US	United States
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WBC	white blood cells
wc	water consumption
wk	week(s)
wt	weight
yr	year(s)

Appendix I

Table 1 Dichlorvos Products Registered in Canada as of 1 June 2017 Excluding Discontinued Products or Products with a Submission for Discontinuation Based on the PMRA's Electronic Pesticide Regulatory System (e-PRS) database

Registration Number	Marketing Class	Registrant	Product Name	Formulation Type	Guarantee
19723	Technical	AMVAC Chemical Corporation	Dichlorvos (DDVP) Technical	Liquid	96%
11819	Commercial	Gardex Chemicals Ltd.	Gardex Vapona Insecticide Industrial Fogging Solution	Emulsifiable concentrate or emulsion	4.65%
23915	Commercial	Loveland Products Canada Inc.	DDVP 20% Insecticide	Emulsifiable concentrate or emulsion	20%
19680	Commercial	Premier Tech Brighton Ltd.	Pro Professional DDVP-20 Ultra-Low Volume Insecticide	Solution	20%
16476	Commercial	Gardex Chemicals Ltd.	Vapona-20 ULV Concentrate	Emulsifiable concentrate or emulsion	20%
21824	Commercial	Plus	Dichlorvos Plus #1 Ready to Use Insecticide	Solution	1.8%
21222	Commercial	Aberdeen Road Company	Vaportape II Insecticidal Strips	Slow-release generator	10%
22027	Domestic	Scotts Canada Ltd.	Home Defense Max No-Pest Insecticide Strip	Slow-release generator	19.2%

Table 2 Registered Commercial Class Uses of Dichlorvos in Canada as of 1 June 2017[1]

Sites	Pests	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Typical Number of Days Between Applications	Supported Use?
				Maximum Single	Maximum Cumulative			
Greenhouse cucumber	Aphids, whiteflies	Emulsifiable concentrate or emulsion	Surface spray	(0.05658 g a.i./m^2)[2]	(0.2829 g a.i./m^2/year)	[5][3]	(73)	Yes
Greenhouse tomato	Aphids, whiteflies	Emulsifiable concentrate or emulsion	Surface spray	(0.05658 g a.i./m^2)	(0.11316 g a.i./m^2/year)	[2]	(182)	Yes
Mushroom house	Sciarid and phorid flies	Emulsifiable concentrate or emulsion	Thermal and mechanical fogging apparatus Space spray - fog	(0.00812 g a.i./m^3)	(0.42224 g a.i./m^3/year)	[52]	(3.5)	Registrant of Reg No. 11819 does not support the use
Greenhouse ornamentals	Aphids, whiteflies	Emulsifiable concentrate or emulsion	Surface spray	(0.05658 g a.i./m^2)	(0.22632 g a.i./m^2/year)	[4]	(91)	Yes
Tobacco in storage	Cigarette beetles, tobacco moths and other insect pests of stored tobacco	Emulsifiable concentrate or emulsion	Thermal and mechanical fogging apparatus or ULV applicator Space spray - fog	(0.066 g a.i./m^3)	(0.396 g a.i./m^3/year)	[6]	[7]	Yes
Tobacco in storage	Cigarette beetles and tobacco moths	Solution	Ultra-low volume applicator or automated fogger Space spray- fog	(0.064 g a.i./m^3)	(0.384 g a.i./m^3/year)	[6]	[7]	Yes
Food processing plants, industrial plants, warehouses, theatres and similar enclosed areas	Flies, mosquitoes, wasps, gnats, fruit flies and other small flying insects as well as exposed stages of almond moth, rice weevils, confused flour beetles, meal moths, cocoa bean moths and other insects that may be infesting packaged or bagged food commodities.	Emulsifiable concentrate or emulsion	Thermal and mechanical fogging apparatus or ULV applicator Space spray- fog	(0.033 g a.i./m^3)	(1.716 g a.i./m^3/year)	[52]	[7]	Yes
Vegetable and fruit crops	Gypsy moth, spruce budworm, forest tent caterpillar, Mediterranean fruit fly, codling moth and other lepidopterous pests.	Slow-release generator	Insecticidal strip	(0.59 g a.i./strips) (2.36 g a.i./ha calculated using 4 strips/ha)	(7.08 g a.i./ha/year)	[3]	[56]	Yes

Sites	Pests	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Typical Number of Days Between Applications	Supported Use?
				Maximum Single	Maximum Cumulative			
Latrines, loading docks, parking areas, refuse areas	Flies, gnats, mosquitoes, fleas, ants and sowbugs	Solution	Ultra-low volume applicator Surface spray	(0.228 g a.i./m^2)	Cannot be calculated	Not stated on the label	Not stated on the label	Yes
Around dwellings and other buildings	Honeybees, paper nest wasps, hornets and yellow jackets	Emulsifiable concentrate or emulsion	Mechanical fogging equipment Space or contact spray	Cannot be calculated	Cannot be calculated	Not stated on the label	Not stated on the label	Registrant of Reg No. 16476 does not support the use
Poultry houses	Flies, gnats, mosquitoes, cockroaches, fleas and sow bugs	Emulsifiable concentrate or emulsion	Mechanical fogging equipment Space or contact spray.	(0.236 g a.i./m^2)	(4.72 g a.i./m^2/year)	[20]	[7]	Registrant of Reg No. 16476 does not support the use
Dairies, piggeries, poultry houses, barns	Flies, mosquitoes and gnats	Solution	Mist fogger Space spray - fog	(0.0174 g a.i./m^3)	(0.348 g a.i./m^3/year)	[20]	[7]	Yes
Food processing plants, industrial plants, theatres and warehouses:	Exposed stages of confused flour beetle, cocoa bean moth, fruit flies, flour beetle, gnats, rice weevil, wasps.	Solution	Automated fogger or ultra-low volume applicator. Space spray - fog	(0.032 g a.i./m^3)	(1.664 g a.i./m^3/year)	[52]	[7]	Yes
Sheds stables, livestock, barns, loafing sheds, pig pens, poultry houses and outdoor areas	Flies, gnats, mosquitoes, cockroaches, fleas, ants and sowbugs	Emulsifiable concentrate or emulsion	ULV applications or diluted for use in ordinary mechanical fogging equipment Space spray or contact spray.	(0.236 g a.i./m^2)	(4.72 g a.i./m^2/year)	20	[7]	Registrant of Reg No. 16476 does not support the use
Sheds stables, livestock, barns, loafing sheds, pig pens, poultry houses and outdoor areas	Flies, gnats, mosquitoes	Solution	Surface spray	(0.228 g a.i./m^2)	(4.56 g a.i./m^2/year)	[20]	[7]	Yes
Outdoor living areas, picnic grounds, backyard areas, patios, latrines, loading docks, parking areas, refuse areas, and other areas around buildings	Flies, gnats, mosquitoes, fleas, ants and sowbugs	Emulsifiable concentrate or emulsion	Surface spray	(0.236 g a.i./m^2)	Cannot be calculated			Registrant of Reg No. 16476 does not support the use

Sites	Pests	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Typical Number of Days Between Applications	Supported Use?
				Maximum Single	Maximum Cumulative			
Outdoor mosquito control	Mosquitoes	Emulsifiable concentrate or emulsion	Mechanical fogging equipment Space or contact spray.	(113.16 g a.i./ha)	Cannot be calculated	Not stated on the label	Not stated on the label	Registrant of Reg Nos. 11819 and 16476 does not support the use
Outdoor mosquito control	Mosquitoes	Solution	Automated fogger or Ultra-low volume applicator Space spray - fog	(109.56 g a.i./ha)	Cannot be calculated	Not stated on the label	Not stated on the label	Yes

1 Table 2 excludes discontinued products or products with an application for discontinuation based on the PMRA's Electronic Pesticide Regulatory System (e-PRS) database.
2 Information indicated in ( ) was calculated by the PMRA, but derived from registered product labels.
3 Information indicated in [ ] was provided by the PMRA, based on previous consultations with crop specialists, in-house information or purchased proprietary information.
4 Information indicated in { } was provided by registrants.

Table 3 Registered Domestic Class Uses of Dichlorvos in Canada as of 1 June 2017[1]

Sites	Pests	Formulation Type	Application Methods and Equipment	Application Rate		Maximum Number of Applications per Year	Typical Number of Days Between Applications	Supported Use?
				Maximum Single	Maximum Cumulative			
For use in unoccupied areas. Not for use in homes except garages, attics, crawl spaces and sheds, occupied for less than 4h/day	Flies, mosquitoes and other small flying insects	Slow-release generator	Resin vaporizer strip	(0.416 g a.i./m^3)[2]	(1.248 g a.i./m^3)	3	Up to four months	Yes
Animal and farm buildings, milk rooms, motels, restaurants, food processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces if areas are occupied for less than 4h/day	Flies, mosquitoes and other small flying insects	Slow-release generator	Resin vaporizer strip	(0.416 g a.i./m^3)	(1.248 g a.i./m^3)	3	Up to four months	Yes
Cottages, cabins and trailer if areas are unoccupied for 4 months following placement of strips	Flies, mosquitoes and other small flying insects	Slow-release generator	Resin vaporizer strip	(0.416 g a.i./m^3	(1.248 g a.i./m^3)	3	Up to four months	Yes

1 Table 2 excludes discontinued products or products with an application for discontinuation based on the PMRA's Electronic Pesticide Regulatory System (e-PRS) database.
2 Information indicated in ( ) was calculated by the PMRA, but derived from registered product labels.

Appendix II Toxicological Information for Health Risk Assessment

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise specified. Depression of PChE is not considered by the PMRA to be a toxicologically adverse effect; it can be viewed as a marker of exposure. Depression of EChE can be viewed as a surrogate for adverse changes in the peripheral nervous tissue in acute and some short-term studies. In studies of longer duration, depression of EChE is not considered by the PMRA to be a toxicologically adverse effect. Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted.

Table 1 Toxicology Profile

Study Type/ Animal/ PMRA #	Study Results
Toxicokinetic Studies	
Metabolism, Oral Mouse, Hamster, Rat, Human **Absorption:** Dichlorvos was rapidly and readily absorbed from the GI tract in the rat. **Distribution:** In rats receiving a single dose of vinyl-labelled dichlorvos, radioactivity was identified in the skin (6-9%), liver (4-6%), gut (2%) and the carcass (12-16%) 96 hrs post-dose. Smaller amounts of radioactivity were found in the blood, brain, fat, heart, kidney, muscle, stomach, large and small intestine. The hamster had a similar profile compared to the rat whereas the mouse had a higher level of administered radioactivity in the carcass (26-34%). In rats receiving a single or repeated dose of ^{14}C-labelled dichlorvos (position of radiolabel unknown) the highest tissue levels of radioactivity were identified in the liver, kidneys, uterus, spleen, lungs, bone and the blood. Low levels of dichlorvos were also found in the fat. In rats receiving a single dose of P-labelled dichlorvos, the time-to-peak radioactivity was 15 mins in the blood and 1 hr in the stomach, intestine, liver and kidney. P-labelled dichlorvos was detected at 7 days in the bone, kidney and liver. **Metabolism**: Major urinary metabolites (>64%) were DMP or MMP with methyl or P-labelled dichlorvos in rats and methyl labelled dichlorvos in mice. The next major metabolite in urine was desmethyl dichlorvos (2-13% in rats, 25% in mice) with minor metabolites being S-methyl-L-cysteine oxide and methylmercapturic acid S-oxide. With vinyl labelled dichlorvos, major urinary metabolites in rats included dichloroethyl glucuronide, 2,2-dichloroethyl-β-D-glucopyranosiduronic acid and desmethyldichlorvos followed by hippuric acid. With higher doses, urea became a more prominent urinary metabolite. Hippuric acid and urea were also identified as minor faecal metabolites. **Excretion:** In rats, vinyl-labelled dichlorvos was excreted in air (16-39%), urine (10-32%) and feces (1-16% of the administered radioactivity) by 96 hrs post-dose. Mice and hamsters showed similar patterns of excretion. Orally dosed humans excreted dichlorvos in air (27% in 8 hrs). Methyl-labelled dichlorvos was excreted	

Study Type/ Animal/ PMRA #	Study Results
similarly in mice and rats by 96 hrs post-dose (urine: 59-65%, air: 15-19%, feces: 3-7% of the administered radioactivity). P-labelled dichlorvos was excreted in rats in the urine (60-70%), air (16%) and feces (11-17%) 7 days post-dose. Excretion was similar between single- and repeat-dose regimes in rats when administered ^{14}C-labelled dichlorvos (position of radiolabel unknown).	
Metabolism, Inhalation Rat, Mouse, Human **Distribution:** Radioactivity in mice exposed by inhalation to ^{14}C-labelled dichlorvos was detected in the liver, lung, kidneys, blood and testes only. Rats exposed to a single-dose of ^{14}C-labelled dichlorvos by inhalation had the highest concentrations of radioactivity in the lung, fat, trachea and kidneys in ♂ and in the brain, blood, trachea and fat in ♀. The kidneys of ♂ contained a significantly higher concentration of dichlorvos than that found in ♀. The relative distribution of radioactivity in the liver, gut, skin and carcass 4 days following exposure was similar to that seen following oral dosing. Radioactivity was not detected in tissues of rats following a low-dose repeat-dose exposure. In humans exposed to ^{14}C-labelled dichlorvos, radioactivity was not detected in blood immediately following exposure. **Metabolism:** Rats exposed to ^{14}C-labelled dichlorvos by the inhalation route had a similar metabolic profile to rats exposed by the oral route. In rats exposed to ^{14}C-labelled dichlorvos the major urinary metabolite was 2,2-dichloroethyl-β-D-glucopyranosiduronic acid (27%), hippuric acid (9%), urea (5%) and desmethyldichlorvos (4%). In humans, dichlorethanol was identified as the major urinary metabolite. **Excretion:** Rats exposed to ^{14}C labelled dichlorvos by the inhalation route had a similar excretion profile to that following oral exposure when expressed in terms of relative amounts of radioactivity in urine, faeces and expired air.	
Metabolism, in vitro PMRA No. 2480298 **T½ in blood:** Rat: 12.6-31.0 mins Rabbit: 1.44-2.2 mins (0.9 mins in plasma) Human: 7.0-10.8 mins (18.0 mins in plasma)	
Acute Toxicity Studies	
Acute Oral Mouse	**LD_{50} = 68-275 mg/kg bw** Mortality within 3 hrs, muscle fasciculations and ataxia within minutes. Insufficient data to determine differences in strain/sex sensitivity or an effect of carrier/solvent. **Highly Toxic.**
Acute Oral Rat	**LD_{50} = 30-110 mg/kg bw** Clinical signs included sluggishness, ataxia, coma, tachypnea, dyspnoea, exophthalmos, ruffled fur, curved position, tremors, chromodacryorrhea, clonic convulsions, lacrimation, prostration, bulging eyes, sialorrhea,

Study Type/ Animal/ PMRA #	Study Results
	muscle fasciculations, trismus, and tonic-clonic muscle spasms of limb muscles, cramps of cheek muscles, sedation and secretion from Harderian glands. Complete recovery in surviving individuals within 1 to 12 days. Mortalities from <1 hr to 24 hrs. Lung edema, liver congestion and gastrointestinal tract bloating noted in animals dying after treatment. **Highly Toxic.**
Acute Oral Rabbit	**LD_{50} = 12.5-74 mg/kg bw** Clinical signs included dyspnea, salivation, asynchronism of extremities, clonic-tonic muscle spasms, exophthalmos and lateral position. Mortality associated with congestion of thymus, lungs and liver and haemorrhage of thymus and stomach. **Highly Toxic.**
Acute Oral Dog, Mongrel	**LD_{50} = 100-316 mg/kg bw** **Highly Toxic.**
Acute Oral Dog, Greyhounds and cross-breeds	≥11 mg/kg bw: ↓ PChE and EChE activity. 22 mg/kg bw: mortality (15 mins to 2.5 hrs post-dosing, associated with hyperpnea, bradycardia, arrhythmia, dyspnea, salivation, tremors, convulsions, urination, diarrhea, ataxia, apprehension, tonic-clonic convulsions, coma and respiratory failure), restlessness, fine muscle fasciculations, hypersensitivity to sound and touch, miosis, vomiting, tenesmus, ↓ BChE activity, generalized pulmonary congestion, hyperaemia (pulmonary, GI tract), cardiovascular changes, haemorrhage (cardiovascular, GI tract), muscle fibre degeneration and necrosis, ↑ serum AST, ALT and CPK, ↑ body temperature, persistent weight loss, ↑ venous Hct and plasma protein. Clinical signs more severe in greyhounds than in crossbreeds.
Acute Oral Dog, Beagle	44 mg/kg bw: significant changes in liver histopathology at 24 hrs (↑ cytoplasmic area, ↓ nuclear area, ↑ number of mitochondria, ↑ SER and RER).
Acute Oral Chicken, New Hampshire	**LD_{50} = 14.8 mg/kg bw** Clinical signs included lethargy, salivation, ataxia and convulsions. **Highly Toxic.**
Acute Dermal Mouse	**LD_{50} = 206-395 mg/kg bw (♂)** **Highly Toxic.**
Acute Dermal Rat	**LD_{50} = 35-265 mg/kg bw** Clinical signs 15 mins to 3 days post-dosing included lethargy, tremors, coma, respiratory difficulties, ↓ body temperature, trismus, tonic-clonic

Study Type/ Animal/ PMRA #	Study Results
	spasm of limb muscles, prostration, exophthalmos, dyspnea and lacrimation. Occasional erythema noted followed by scab formation. Mortality within 1 to 7 days post-dosing often associated with petechiae and/or erosion of GI tract, bloody GI tract contents, petechiae of thymus and stomach, mucous in stomach with yellowish discolouration, dilation of renal pelvis, blood in bladder contents, acute congestion (liver, spleen and kidney), bloated intestines, inflamed peritoneum, enlarged livers, bloated or slack intestines. **Highly Toxic.**
Acute Dermal Rabbit	**LD_{50} = 125-205 mg/kg bw** **Highly Toxic.**
Acute Inhalation Mouse, CF1	**LC_{50} > 0.218 mg/L** (4-hrs, head-only vapour exposure) Clinical signs included tremors, lethargy, hind-limb paresis and splayed gait with recovery by day 2. **Moderately Toxic.**
Acute Inhalation Rat	**LC_{50} = 0.230 mg/L** (head-only aerosol exposure, duration N/S) **Moderately Toxic.** **LC_{50}= 0.523/0.447 mg/L (♂/♀)** (4-hrs, head-only aerosol exposure) **Slight to Moderate Toxicity**. Clinical signs up to 7 days post-dosing included lethargy, ataxia, tremors, hypopnea, hypothermia, bloody eye and nose encrustations, respiratory difficulties, piloerection, hypersensitivity to noise, bristling, ungroomed coat, reduced motility, high gait, weakness, convulsions, recumbence on side, apathy and dyspnea. Other effects included ↓ bwg. Mortality occasionally associated with signs of respiratory failure, distended lung, edematous and pale, patchy liver with lobulation, pale spleen and kidney, hyperaemia of the glandular stomach and serosa of small intestine, blood and mucus in the gut at autopsy; lung haemorrhage and/or bloody discharge in trachea (♂).
Acute Inhalation Rat	**LC_{50} > 0.116 mg/L** (4-hr, head-only vapour exposure) Clinical signs included bristling, ungroomed coat, reduced motility and high gait. **Moderately Toxic**
Eye Irritation Rabbit, NZW	0.1 mL: mortality within 7 mins, lethargy, convulsions, muscle contractions and immobility. No eye observations made.
Eye Irritation Rabbits, NZW	Ocular effects: slight corneal opacity, slight to severe conjunctival redness and swelling, ↑ tear flow (all animals, recovery in surviving animals within 14 to 21 days). Adverse signs included mortality at 25

Study Type/ Animal/ PMRA #	Study Results
	mins and miosis, muscular fasciculations, tremors, staggering gait, recumbence on stomach, cyanosis, salivation, tachypnea and bronchosecretion in all animals immediately after administration. **Severe irritant.**
Skin Irritation Rabbits, NZW	0.5 mL: slight to moderate erythema and slight swelling (all rabbits 48 hrs post-dosing). Erythema declined in 2 rabbits to slight after 7 days but increased to moderate in the third rabbit. After 14 days this rabbit showed slight erythema with no other effects evident in other animals. **Slight irritant.**
Skin Irritation Rabbit	0.2 mL: mortality within 2 hrs associated with tremors and convulsions. Surviving animals displayed tremors, ataxia (within 3 hrs, recovery by day 2). Slight erythema (at 1 hr) and slight to moderate (at 48 hrs until day 7) and slight edema (24 hrs post-patch removal). Complete recovery within 14 days. **Slight irritant.**
Skin Irritation Rabbit	0.5 mL: mortality within 1 hr (all animals).
Skin Sensitization Guinea Pig	**Positive for skin sensitization (maximization assay).**
Short-Term Toxicity Studies	
90-day Range-finding, Oral (gavage) Mouse, B6C3F1	≥80 mg/kg bw/day: ↑ mortality. No effects on bw or clinical signs in surviving animals. No gross or histopathological effects noted.
6-wk Oral (gavage) Rat, F344	≥40 mg/kg bw/day: ↑ mortality, ↓ bw (♀). 80 mg/kg bw/day: ↓ motor activity, ↓ liver, heart, lung and kidney wt; ↓ bw, ↓ testes wt (♂).
45-day Oral (dietary) Rat, Albino	≥8.35 mg/kg bw/day: ↓ fc (transient), ↓ Hgb, ↑ blood glucose, ↓ whole blood ChE. 16.6 mg/kg bw/day: ↑ mortality, muscular fibrillation, laboured breathing, diarrhea, ↑ micturition frequency, ↓ absolute spleen wt, ↓ WBC levels
90-day Range-finding, Oral (gavage) Rat, F344/N	≥8 mg/kg bw/day: ↓ terminal bw (5%) (♀). ≥16 mg/kg bw/day: ↑ mortality, trembling and inactivity prior to death. No treatment-related gross or histopathological effects.
90-day Oral (dietary) Rat, Sherman	≥0.4 mg/kg bw/day: transient ↓ PChE activity. ≥3.5 mg/kg bw/day: ↓ PChE and EChE activity (recovery by day 90).

Study Type/ Animal/ PMRA #	Study Results
	≥14.2 mg/kg bw/day: persistent, dose-dependent ↓ EChE activity. Note: No data on stability or storage of diet formulation. Other studies show that dichlorvos is not stable in diet; therefore, there is doubt as to whether the reported achieved dosages are accurate. Therefore, study is only considered qualitatively in current re-evaluation. **Supplemental.**
90-day Oral (gavage) Rat, Sprague-Dawley	**NOAEL = 0.1 mg/kg bw/day** ≥1.5 mg/kg bw/day: ↓ EChE activity; transient ↓ PChE activity, ↓ RBC, Hgb and Hct (♂). 15 mg/kg bw/day: salivation, urine stains, ↓ BChE and PChE activity; ↑ cholesterol, ↑ relative liver wt (♂); ocular effects (phthisis bulbi - equivocal), slight tubular mineralization in kidneys, ↓ RBC, Hgb and Hct, ↑ MCV (♀).
21-day Oral (capsule) Monkey, Rhesus	1-16 mg/kg bw/day: ↓ appetite, ↑ diarrhea, emesis and salivation, ↓ PChE (no dose-response, returned to normal within 3 wks) and EChE activity (no dose-response, returned to normal within 2 months). ↑ incidence of clinical signs with ↑ duration of dosing.
10-day Dermal Monkey, Rhesus	≥50 mg/kg bw/day: ↑ mortality, nervousness, gritting of teeth, incoordination, muscle fasciculations, excessive salivation, laboured breathing, miosis and inability to move within 10 to 20 mins after first application. 75 mg/kg bw/day: ↓ PChE activity. Note: ChE data only reported for mid-dose. Assumed that only PChE activity was measured.
Chronic Toxicity/Oncogenicity Studies	
2-yr Chronic Toxicity/ Carcinogenicity, Oral (gavage) Mouse, B6C3F1	**LOAEL = 10/20 mg/kg bw/day** ♂/♀ ≥10 mg/kg bw/day (♂ only): ↓ PChE and EChE activity, ↑ squamous cell forestomach papilloma (statistically significant dose-related trend, not significant in pairwise comparisons) (♂). 20 mg/kg bw/day (♂ and ♀): ↑ squamous cell forestomach carcinoma or papilloma (♂); ↓ PChE activity, transient ↓ EChE activity (♀). 40 mg/kg bw/day (♀ only): ↑ squamous cell forestomach carcinoma or papilloma (♀). Note: Positive result for carcinogenicity may have been confounded by use of corn oil vehicle.

Study Type/ Animal/ PMRA #	Study Results
	Positive for carcinogenicity.
2-yr Chronic Toxicity/ Carcinogenicity, Oral (gavage) Rat, F344	**LOAEL = 4.14 mg/kg bw/day** 4.14 mg/kg bw/day: ↓ PChE and EChE activity, ↑ pancreatic adenoma, ↑ leukemia (lymphocytic, monocytic, mononuclear or undifferentiated); cytoplasmic vacuolation of liver and adrenal cortex (not statistically significant) (♂); ↑ mammary gland fibroadenomas or adenomas (♀). 7.82 mg/kg bw/day: lung alveolar bronchiolar adenoma (♂); ↑ pancreatic atrophy and adenoma (♀). Note: Exception for pancreatic tumours in ♂s, all cancer related findings were considered equivocal for one or more of the following reasons: lack of dose-response, lack of statistical significance in trend test, lack of statistical significance in pairwise comparisons and/or incidence of finding within historical control range. **Equivocal evidence of carcinogenicity may have been confounded by use of corn oil vehicle.**
70-day Leukaemia Transplant Study, Oral (gavage) Rat, F344 Animals sacrificed 70 days post-transplant	16 mg/kg bw/day (with transplant): ↑ mortality. Severity of MCL in transplant recipients correlated with tumour growth rates. Rats dosed with dichlorvos developed the disease earlier and the rate of tumour progression increased.
80-wk Carcinogenicity, Oral (dietary) Rat, Osborne-Mendel All animals maintained on control diet for 30-31 wks prior to sacrifice	7.5 mg/kg bw/day: ↑ incidence of clinical signs (during 2nd year, particularly in high-dose ♀s), ↑ alveolar macrophages, ↑ myocardial fibrosis, ↑ hyperplasia of bile duct; suppurative inflammation of the prostate, follicular cell hyperplasia (♂); ↑ fatty metamorphosis of liver (♀). 16.3 mg/kg bw/day: ↓ bwg (10%), malignant fibrous histiocytoma of subcutis (significant positive trend) (♂). Note: Current re-evaluation does not consider this study to be an adequate assessment of carcinogenic potential due to an insufficient number of control animals and the fact that achieved dosages were not determined. The short duration of study may have precluded progressive changes. This study is retained for qualitative information on chronic toxicity. **Supplemental.**
1-yr Chronic Toxicity, Oral (capsule) Dog, Beagle	**NOAEL = 0.05 mg/kg bw/day** No treatment-related effect on fc, ophthalmology, gross pathology or histopathology.

Study Type/ Animal/ PMRA #	Study Results
0.1 mg/kg bw/day dose lowered to 0.05 mg/kg bw/day on day 22 due to inhibition of plasma ChE activity noted after 12 days	≥0.05 mg/kg bw/day: ↓ EChE activity (6 wks only)*. ≥0.1 mg/kg bw/day: ↓ PChE activity, ↓ EChE activity (day 12). ≥1.0 mg/kg bw/day: ↓ BChE activity (♂). 3.0 mg/kg bw/day: ↑ emesis (1 animal), ↓ BChE activity (♀). *↓ EChE activity at 0.05 mg/kg bw/day believed to be a residual effect from dosing at 0.1 mg/kg bw/day.
2-yr Inhalation (vapour, continuous exposure) Rats, Carworth Farm E	≥0.00005 mg/L: slightly ↓ EChE activity (12%) (♀). ≥0.00048 mg/L: ↓ PChE and EChE activity, slightly ↓ BChE; ↓ bw, ↓ heart wt (♂); ↓ kidney wt (♀). 0.0047 mg/L: ↓ mortality, ↑ AST and ALT, ↓ plasma chloride; ↓ relative spleen wt, ↓ kidney wt (♂). **Supplemental due to deficiencies (high mortality in ♂ controls, uncertainties regarding achieved dose, lack of report detail, lack of hematology, clinical chemistry and ChE activity measurements).**
Genotoxicity Studies	
Mitotic Non-disjunction and Crossing Over A. nidulans	3 studies, 3 positive. 2 studies said to be poorly reported.
Recombinant Assay B. subtilis: H17 Rec+; M45 Rec-	B. subtilis H17 Rec+: Negative. M45 Rec-: Positive.
Forward Mutation A. nidulans: strain 35 S. coelicolor: A 3(2) his A1 E.coli: K12(5-MT); B Gal RS	5 studies, 5 positive.
Reverse Mutation *S. pombe*: SP-198 ade 6-60/rad 10-198/h *C. freundii*: 425 *E. aerogenes* *P. aeroginusa*: PAO	*S. pombe*: 1 study, 1 positive. *C. freundii*: 1 study, 1 positive. *E. aerogenes*: 1 study, 1 positive. *P. aeroginusa*: 1 study, 1 positive. *K. pneumoniae*: 1 study, 1 positive.

Study Type/ Animal/ PMRA #	Study Results
K. pneumoniae *S. marcescens*: Hy/alpha 13; Hy/alpha 21	*S. marcescens*: 2 studies, 2 positive. Hy/alpha 13: 1 study, 1 positive. Hy/alpha 21: 1 study, 1 positive.
Reverse Mutation *S. typhimurium*: TA98; TA100; TA1530; TA1531; TA1532; TA1534; TA1535; TA1536; TA1537; TA1538; his C117; G46 *E. Coli*: B/r WP2; WP2 hcr; SR714; CM561; CM 571; CM611; WP2; WP2 uvr A; K12HfrH; CM 881; WP2 hcr+/hcr-; WP 67; WP12	*S. typhimurium*: 34 studies, 9 positive, 23 negative, 2 equivocal. TA 98: 3 studies, 3 negative. TA 100: 3 studies, 3 positive. TA 1530: 1 study, 1 positive. TA 1531: 1 study, 1 negative. TA 1532: 1 study, 1 negative. TA 1534: 1 study, 1 negative. TA 1535: 7 studies, 3 positive, 2 negative, 2 equivocal. TA 1536: 4 studies, 1 positive, 3 negative. TA 1537: 5 studies, 5 negative. TA 1538: 5 studies, 5 negative. his C117: 2 studies, 1 negative, 1 positive. G46: 1 study, 1 negative. *E. Coli*: 21 studies, 14 positive, 7 negative: Br WP2: 2 studies, 2 positive. WP2 hcr: 1 study, 1 positive. SR714: 1 study, 1 positive. CM561: 2 studies, 1 positive, 1 negative. CM 571: 2 studies, 2 negative *. WP2 hcr+/hcr-: 1 study, 1 positive. CM 611: 2 studies, 2 negative*. WP2: 4 studies, 3 positive, 1 negative. WP2 uvr A: 2 studies, 2 positive. K12HfrH: 1 study, 1 positive. CM881: 1 study, 1 positive. WP67: 1 study, 1 positive. WP12: 1 study, 1 negative. *Positive control yielded negative response in one study.
Gene Conversion *S. cerevisiae*: D4; 632/4	3 studies, 2 positive, 1 negative (poorly reported study). D4: 2 studies, 2 positive. 632/4: 1 study, 1 negative.
In vitro Unscheduled DNA Synthesis Human Epithelial-like Cells Human kidney derived heteroploid cell line Human (cell line unstated)	3 studies, 2 positive, 1 negative Human Epithelial-like Cells: significant ↑ in net nuclear gains. Human kidney derived heteroploid cell line: negative Human (cell line unstated, non-standard study): significant ↑ in ^{3}H-thymidine uptake

Study Type/ Animal/ PMRA #	Study Results
In vitro DNA Alkylation, in isolation *E. Coli* HeLa Cells	Dichlorvos can methylate DNA, RNA and protein. DNA alkylation products were N7-methylguanine (the major adduct), N3-methylguanine, N1-methyladenine, O^6-methylguanine. Two studies claimed significant labelling of proteins, 20-30 times greater than DNA.
DNA Damage and Repair, Spot Test or Plate Incorporation *E. coli*: W3110polA+/polA- *B. subtilis* P. mirabilis: PG 273; PG713	E. coli: W3110polA+/polA-: 1 study, 1 positive. *B. subtilis*: 1 study, 1 positive. *P. mirabilis*: PG 273: 1 study, 1 positive. PG713: 1 study, 1 positive.
DNA Damage and Repair, Liquid Preincubation tests *E. coli*: pol; exr; uvr mutant strains	pol: positive. exr: positive. uvr: negative
DNA Strand Breaks *E. coli*: K-12CR34Co1E1; WP67	2 studies, 2 positive. K-12CR34Co1E1: positive. WP67: positive without activation.
In vitro DNA Strand breaks Chinese Hamster V79 cells	Positive. Negative at lower concentrations.
In vitro Induction of DNA Breaks and DNA Repair T-Cells (human kidney heteroploid cell line)	Negative. No change in rate of incorporation of tritiated thymidine. Does not damage DNA or hinder DNA repair.
In vitro Viral Transformation Syrian Hamster Embryo Cells/adenovirus SA7	Positive.
In vitro Gene Mutation Chinese Hamster V79 cells: HPRT locus, azaguanine/ ouabain resistance Chinese Hamster Ovary Cells: HPRT locus Mouse Lymphoma cells L5178Y TK	Chinese Hamster V79 cells HPRT locus, azaguanine/ouabain resistance: 2 studies, 2 negative. Chinese Hamster Ovary Cells, HPRT locus: 1 study, 1 positive (without S9). Mouse Lymphoma: 3 studies, 3 positive.

Study Type/ Animal/ PMRA #	Study Results
In vitro Sister Chromatid Exchange Primary rat tracheal epithelial cells	Positive from 10 µg/mL. 50% cell death at 80 µg/mL.
In vitro Sister Chromatid Exchange Chinese Hamster Ovary Cells	4 studies, 4 positive.
In vitro Chromosomal Aberrations Chinese Hamster V79 cells Chinese Hamster Ovary cells Chinese Hamster Lung cells Human Lymphocytes EUE Human cells	8 studies, 6 positive, 2 negative. Chinese Hamster Ovary Cells: 1 study, 1 positive. Chinese Hamster V79 cells: 1 study, 1 positive. Chinese Hamster Lung cells: 2 studies, 2 positive. Human Lymphocytes: 3 studies, 1 positive, 2 negative (One negative study reported to have deficiencies in methodology. Metaphases only examined after 50 - 70 hr). EUE Human cells: 1 study, 1 positive.
In vitro DNA Damage - Comet Assay Chinese Hamster Ovary cells PMRA No. 2489926	≥0.01 µM: ↑ DNA damage (tail moment (arbitrary units), tail DNA (%) and tail length (µM)) following exposure for 3 hrs. ≥1,000 µM: ↓ mitochondrial activity in CHO cells. Positive.
In vitro DNA Sedimentation Coefficient Calf thymus DNA	Positive.
In vitro DNA Resistance to Micrococcal Chinese Hamster Ovary cells	Positive.
In vitro Micronucleus Assay Human lymphoblastoid AHH-1 cells **PMRA No.** 2489918	≥10 ng/mL: slightly ↑ frequency of cells showing chromosome non-disjunction for chromosomes 7 and 11 ≥20 ng/mL: ↑ number of micronucleated cells and total micronuclei in AHH-1 cells, ↑ CREST-positive micronuclei in AHH-1 cells ≥40 ng/mL: ↑ number of trypan blue-positive cells, ↑ % of mononucleated cells in cytochalasin B-treated cultures, ↓ % of binucleated and polynucleated cells in cytochalasin B-treated cultures, ↓ fraction of AHH-1 cells in the S phase with majority of cells in the G1 or G2/M phase of the cell cycle, significant induction of apoptosis

Study Type/ Animal/ PMRA #	Study Results
	Positive for aneuploidy.
In vivo Crossover Recombination D. melanogaster	8 Studies, 3 positive (using 1 to 5 ppm), 5 negative (at doses of up to 6.0 × 10^{-3} mM).
In vivo Micronucleus and Chromosomal Aberration Assays Swiss albino mice (♂) - bone marrow cells **PMRA No.** 2489922	Micronucleus Assay: Negative. Chromosome Aberration Assay: Negative.
In vivo Host-mediated Assay *S. typhimurium*, 64-320 in Swiss mouse (oral) *S. typhimurium*, G46 His- in NMRA mice (subcutaneous) *S. cerevisiae*, D4 in CF1 mice (oral, inhalation) *S. marcescens*, a 21 Leu- in NMRI mice (subcutaneous)	4 Studies, 4 negative. Note: administered orally, subcutaneously and by inhalation.
In vivo Dominant Lethal Mouse: CF1(gavage, inhalation); ICR/Ha Swiss (gavage, i.p.); Q (drinking water, gavage, i.p.); CD1 (IP); unstated strain (i.p.)	10 studies, 10 negative. Note: administered via oral, inhalation and intraperitoneal routes.
In vivo Sister Chromatid Exchange Mouse; B6C3F1 (♂), peripheral lymphocytes, bone marrow cells Chinese Hamster Ovary Cells	4 studies, 3 negative, 1 positive. Mouse: 3 studies, 3 negative. Hamster: 1 study, 1 positive.
In vivo Micronucleus Test Mouse (i.p.) Mouse, HRA/Skh, hairless,	5 studies, 3 negative, 2 positive. Mouse: 4 studies, 3 negative, 1 positive. Mouse HRA/Skh, hairless, skin keratinocytes: 1 study, 1 positive.

Study Type/ Animal/ PMRA #	Study Results
skin keratinocytes (dermal) Mouse, CD1 bone marrow micronucleus/hair follicle nuclear aberration assay (dermal) Mouse, Swiss Albino, bone marrow (i.p.) Chinese Hamster Ovary Cells	**Supplemental study.** Hamster: 1 study, 1 positive.
In vivo Chromosomal Aberrations Chinese Hamster, bone marrow cells (oral, inhalation) Chinese Hamster, spermatocytes (oral, inhalation) Mouse, ICR, bone marrow and spermatogonial cells (oral) Mouse, Q, bone marrow cells (drinking water, IP) Mouse, B6C3F1, bone marrow cells (♂) (i.p.) Mouse, CF1, bone marrow cells (inhalation) Mouse, Q, spermatocytes (drinking water, i.p.) Mouse, CF1, spermatogonia/ spermatocytes (drinking water, i.p., inhalation)	15 studies, 15 negative. Chinese Hamster, bone marrow cells: 2 studies, 2 negative. Chinese Hamster, spermatocytes: 2 studies, 2 negative. Mouse, ICR, bone marrow and spermatogonial cells: 1 study, 1 negative. Mouse, Q, bone marrow cells: 3 studies, 3 negative. Mouse, B6C3F1, bone marrow cells: 1 study, 1 negative. Mouse, CF1, bone marrow cells: 1 study, 1 negative. Mouse, Q, spermatocytes: 2 studies, 2 negative. Mouse, CF1, spermatogonia: 3 studies, 3 negative. Note: administered via oral, inhalation and intraperitoneal routes.
In vivo DNA Strand Breaks Rat, Wistar, rat liver cell DNA (i.p.)	Negative.
In vivo Unscheduled DNA Synthesis	2 studies, 2 negative.

Study Type/ Animal/ PMRA #	Study Results
Mouse, B6C3F1, forestomach Rat, F 344, hepatocytes	Mouse, B6C3F1, forestomach: negative. Rat, F 344, hepatocytes: negative.
In vivo DNA Damage - Comet Assay Mouse, ICR (♂) PMRA No. 2480293	100 mg/kg bw: positive. **Supplemental due to lack of vehicle control and assessment of cell viability.**
In vivo DNA Binding Mouse, NMRI (♂)	i) ^{14}C-[methoxy]-dichlorvos for 2 hrs, inhalation, urine collected for 48 hrs: Urinary ^{14}C-N7-methylguanine comprised 0.007-0.010% of total urinary radioactivity. ii) ^{14}C-[methoxy]-dichlorvos or ^{3}H-[methoxy]-dichlorvos, injection, and urine collected for 48 hrs: urine contained approximately 0.002-0.004% of total dose as ^{14}C-N7-methylguanine.
In vivo DNA Binding Rat, CB hooded (i.p.)	10 mg/kg bw: no ↑ in nucleic acid derivatives.
In vivo DNA Alkylation Mouse, CBA PMRA No. 2480299	1.9 µmol/kg bw ^{14}C-[methoxy]-dichlorvos, i.p. Degree of alkylation of N7 guanine in DNA from liver, spleen, lung, testes, kidney, brain and heart amounted to 8×10^{-13} mol methyl/g DNA.
In vivo DNA Alkylation Rat, R Strain (♂)	900 µCi ^{14}C-[methoxy]-dichlorvos/kg, i.p., urine collected for 4 days 59% of radioactivity recovered in urine. 1.8 nCi (0.0008% of the dose) of administered radioactivity excreted as 1-methylnicotinamide. Adducts of N7-methylguanine and N3-methyl adenine combined for a total of 14.4 nCi over 4 days.
In vivo DNA Alkylation, Inhalation Rat, CFE (♂) PMRA No. 2534672	Dichlorvos did not methylate the nucleic acids of mammalian tissues at a concentration of 0.064 µg/L (113 Ci/mol) for 12 hrs. **Supplemental due to the lack of concurrently run negative and positive controls for the assessment of specific radioactivity in the DNA, RNA or protein in soft tissues.**
In vivo DNA Methylation Mouse (♂)	4, 8 mg/kg ^{14}C-[methoxy]-dichlorvos, i.p., urine collected over 24 hrs Low levels of radiolabelled N7-methylguanine recovered from hepatic nucleic acid. 0.25% of applied dose in DNA, 0.63% in RNA. Concentration of radioactivity was 0.53, 0.42, 0.014 µg ^{14}C/mg of RNA, DNA and protein, respectively. 5.2% of total urinary radioactivity in purine fraction. 0.83% identified as N7-methylguanine.
In vivo DNA damage	≥0.15 ng/mL: ↑ reactive oxygen species generation, superoxide

Study Type/ Animal/ PMRA #	Study Results
D. melanogaster (pre- and post-replication DNA repair deficient mutants) PMRA No. 2489921	dismutase activity, catalase activity and malondialdehyde content, slightly ↑ DNA damage in repair proficient larvae, ↑ migration of DNA in midgut cells of pre-replication repair deficient mutants (mei-9, mus201 and mus207), slightly ↑ oxidative DNA damage 1.5 ng/mL: ↑ DNA damage in repair proficient larvae, ↑ migration of DNA in the midgut cells of post-replication repair deficient mutants (mei-41 and mus209), ↑ oxidative DNA damage Positive for damage to DNA by alkyl modifications and oxidative DNA damage.
Reproductive/Developmental Toxicity Studies	
2-Generation Reproductive, Oral (drinking water) Rat, Sprague-Dawley 10 wks continuous exposure prior to initial mating, minimum 11 wks exposure with subsequent generations	**Parental** **Parental LOAEL = 0.5 mg/kg bw/day** ≥0.5 mg/kg bw/day: ↓ EChE and slightly ↓ BChE activity; ↓ PChE activity (♂). ≥1.9 mg/kg bw/day: ↓ BChE activity; ↓ PChE activity (♀). 8.3 mg/kg bw/day: ↓ wc. **Reproductive** **Reproductive NOAEL = 2.3 mg/kg bw/day** 8.3 mg/kg bw/day: ↓ % of females with estrous cycle, ↑ % of females with abnormal cycling, ↓ dams bearing litters, ↓ fertility and pregnancy indices. **Offspring** **Offspring NOAEL = 2.3 mg/kg bw/day** 8.3 mg/kg bw/day: slightly ↓ mean pup wt, slightly ↓ offspring survival. Note: ChE assessed in F_0 and F_1 at terminal sacrifice.
Developmental, Oral (gavage) Mouse, CF-1	**Maternal** 60 mg/kg bw/day: ↓ bwg. **Developmental** No adverse effects. **Supplemental.**
Developmental, Oral (gavage) Rat, Sprague-Dawley	**Maternal** **Maternal NOAEL = 3 mg/kg bw/day** 21 mg/kg bw/day: tremors, ↓ bwg, fc and fe. Maternal lethality (2/8) noted at 30 mg/kg bw/day in pilot study. **Developmental** **Developmental NOAEL = 21 mg/kg bw/day (HDT)** No adverse effects.

Study Type/ Animal/ PMRA #	Study Results
	Note: ChE not measured.
Developmental, Inhalation (whole body, continuous exposure) Rat, Carworth Farm E	**Maternal** ≥0.00025 mg/L (≈0.26 mg/kg bw/day): ↓ general activity. ≥0.00125 mg/L: ↓ PChE, EChE and BChE activity. **Developmental** No adverse effects. **No evidence of teratogenicity.** **Supplemental.**
Developmental Range-finding, Oral (gavage) Rabbit, NZW	**Maternal** ≥1.0 mg/kg bw/day: ↓ PChE and EChE activity. 10 mg/kg bw/day: ↑ mortality (5/8), clinical signs, ↓ bwg. **Developmental** 10 mg/kg bw/day: slightly ↓ bw.
Developmental, Oral (gavage) Rabbit, NZW	**Maternal** **Maternal NOAEL = 0.1 mg/kg bw/day** ≥2.5 mg/kg bw/day: ↑ mortality, ↓ bwg and liver wt. 7.0 mg/kg bw/day: ↓ fc, ataxia (all animals), prone positioning, tremors, excitation, salivation, diarrhea and difficulty breathing. **Developmental** **Developmental NOAEL = 7.0 mg/kg bw/day (HDT)** No adverse effects.
Developmental, Inhalation (whole body, continuous exposure) Rabbit, Dutch High-dose eliminated from study due to 90% lethality	**Maternal** ≥0.00025 mg/L (≈0.13 mg/kg bw/day): slightly ↓ PChE, EChE and BChE activity. ≥0.00125 mg/L: ↓ PChE, EChE and BChE activity. ≥0.0020 mg/L: ↑ mortality (1/20, day 2 to 3 or day 23) (ChE not assessed). 0.0040-0.0066 mg/L: ↑ mortality or sacrifice in extremis (6/20) (ChE not assessed). 0.00625 mg/L: 90% lethality, anorexia, ataxia, lethargy, muscular tremors, mucous nasal discharge and diarrhea (ChE not assessed). **Developmental** 0.0040 mg/L: slightly ↓ mean fetal wt.

Study Type/ Animal/ PMRA #	Study Results
	Supplemental.
Neurotoxicity Studies	
Acute Cholinesterase Inhibition, Oral (gavage) Rat, Sprague-Dawley (young adults) Sacrificed on days 1, 8 and 15 PMRA No. 2502261	No effects on clinical signs of toxicity, body weight or EChE activity at 1.0 mg/kg bw. 1.0 mg/kg bw: ↓ BChE activity (study day 1: 14.6%) (♂). **Supplemental.**
Acute Cholinesterase Inhibition, Oral (gavage) Rat, Wistar (young adults) ChE examined 1 hr post-dosing and on days 8 and 15 days PMRA No. 2502262	**BChE:** **BMD$_{10}$ = 3.16-4.35/2.15-2.42♂/♀; BMDL$_{10}$ = 2.13-3.37/1.46-1.98 mg/kg bw ♂/♀** **EChE:** **BMD$_{20}$ = 5.33/2.73 ♂/♀; BMDL$_{20}$ = 2.76/2.01 mg/kg bw ♂/♀** ≥1.0 mg/kg bw: ↓ BChE activity (study day 1: cerebellum, cortex, half-brain, remainder of the brain; study day 8: cortex, hippocampus) (♀). ≥5.0 mg/kg bw: ↓ EChE activity (study day 1); ↓ BChE activity (study day 1: cerebellum, cortex, hippocampus, half-brain, remainder of the brain; study day 8: half-brain) (♂); ↓ BChE activity (study day 1: hippocampus; study day 8: cerebellum) (♀). 15 mg/kg bw (♀ only): ↑ incidence of fasciculations and miosis 1 hr post-dosing (1♀), ↓ BChE activity (study day 8: remainder of the brain) (♀). 0 35 mg/kg bw (♂ only): animals sacrificed within 1 hr of dosing for humane reasons (4/9), ↑ incidence of clinical signs (↓ activity, salivation, fasciculations, gasping, reduced splay and righting reflexes, stained around nose, curved spine).
Acute Cholinesterase Inhibition, Oral (gavage) Rat, Wistar, pre-weaning (PNDs 8, 15 and 22) Sacrificed 1 hr post-dosing at estimated time-of-peak effect PMRA No. 2502264	**BChE:** **PND8: BMD$_{10}$ = 1.49/1.99 mg/kg bw ♂/♀; BMDL$_{10}$ = 1.40/1.76 mg/kg bw ♂/♀** **PND15: BMD$_{10}$ = 1.7/1.6 ♂/♀; BMDL$_{10}$ = 1.56/1.37 mg/kg bw ♂/♀** **PND22: BMD$_{10}$ = 1.81/1.78 ♂/♀; BMDL$_{10}$ = 1.65/1.56 mg/kg bw ♂/♀** **Combining age groups:** BChE BMD/BMDL$_{10}$ = 1.775/1.635 mg/kg bw (♀); while ♂ values indicated statistical difference with age (BMDs: 1.486-1.813 mg/kg bw, BMDLs: 1.385-1.665 mg/kg bw) they were not deemed biologically different **EChE:**

Study Type/ Animal/ PMRA #	Study Results
	PND8: BMD$_{20}$ = 3.35/4.6 ♂/♀; BMDL$_{20}$ = 2.91/3.69 mg/kg bw ♂/♀ **PND15: BMD$_{20}$ = 2.85/0.41 ♂/♀; BMDL$_{20}$ = 1.69/0.04 mg/kg bw ♂/♀** **PND22: BMD$_{20}$ = 2.1/2.88 ♂/♀; BMDL$_{20}$ = 0.93/2.13 mg/kg bw ♂/♀** **Combining age groups:** EChE BMD/BMDL$_{20}$ = 2.714/1.77 mg/kg bw (♂); 2.971/1.705 mg/kg bw (♀) ≥1.0 mg/kg bw: ↓ EChE activity (PND 8 ♀s: 22%, PND 15 ♀s: 27%); ↓ BChE activity (PND 22 ♀s: 13%). ≥5.0 mg/kg bw: ↓ BChE activity (PND 8 ♂s: 26% and ♀s: 22%, PND 15 ♂s: 28% and ♀s: 27%, PND 22 ♂s: 31% and ♀s: 25%); ↓ EChE activity (PND 8 ♂s: 26% and ♀s: 31%, PND 15 ♂s: 30% and ♀s: 39%, PND 22 ♂s: 35% and ♀s: 29%). 15 mg/kg bw: slight tremors (PND 8: 1♂ and 1♀, PND 22: 1♀), ↓ BChE activity (PND 8 ♂s: 65% and ♀s: 54%, PND 15 ♂s: 61% and ♀s: 61%, PND 22 ♂s: 58% and ♀s: 60%) and EChE activity (PND 8 ♂s: 62% and ♀s: 56%, PND 15 ♂s: 53% and ♀s: 57%, PND 22 ♂s: 49% and ♀s: 45%).
Acute Cholinesterase Inhibition, Oral (gavage) Rat, Wistar, pre-weaning (PND15) and young adult (PND42) (♀) Sacrificed 1, 3, 8, 24 and 72 hrs post-dosing PMRA No. 2480293	15 mg/kg bw: highest level of inhibition of EChE and BChE activity 1 hr post-dosing in both pre-weaning and young adult rats (PND 15: BChE: 59%, EChE: 53%; PND 42: BChE: 53%, EChE: 46%), significant inhibition of EChE and BChE activity still noted 3 hrs post-dosing. Signs of recovery were noted for EChE and BChE inhibition 8 hrs post-dosing. Complete recovery noted in PND 15 rats by 72 hrs post-dosing whereas residual inhibition was apparent 72 hrs post-dosing in PND 42 rats.
Acute Neurotoxicity Range-finding, Oral (gavage) Rat, Sprague-Dawley Observations made up to 1 day post-dosing only	≥1.0 mg/kg bw: gait alterations (♂). ≥20 mg/kg bw: gait alterations (♀). ≥30 mg/kg bw: ↑ whole body tremors, reduced or absent forelimb/ hindlimb grasp strength, constricted pupil and exophthalmos. 80 mg/kg bw: ↑ mortality (♂). Time-to-peak effect of 15 to 30 mins. No clinical signs 24 hrs post-dosing. **Supplemental.**
Acute Neurotoxicity, Oral (gavage) Rat, Sprague-Dawley	**NOAEL = 0.5 mg/kg bw** 35 mg/kg bw: alterations in FOB (whole body tremors, reduced or absent forelimb/hind limb grasp, ↑ mean time to first step, impaired

Study Type/ Animal/ PMRA #	Study Results
FOB conducted pre-test, 15 mins, 7 and 14 days after treatment	mobility and gait, ↓ arousal and rearing, absence of touch response, absence of tail pinch and pupil response, impaired air righting reflex, ↓ hindlimb resistance, impaired rotarod performance, ↑ duration of catalepsy and ↓ motor activity), constricted pupils and exophthalmos, altered posture, clonic convulsions, salivation, ↓ motor activity, catalepsy and ↓ body temperature, ↑ eye prominence, ↓ muscle tone, altered respiration, pale skin, poor grooming; absence of approach response (♂). 75 mg/kg bw: ↑ mortality, reddened corticomedullary junction in kidney in dead animals, absence of approach response, lack of response to olfactory stimuli, ↓ grip strength, ↑ hindlimb footsplay. Recovery evident for all parameters by Day 7. **No neuropathology findings.** **Note: Cholinesterase measurements not performed.**
7-Day Repeat-dose Cholinesterase Inhibition, Oral (gavage) Rat, Wistar, pre-weaning (PND12) and young adults (PND42) Sacrificed 1 hr following the last dose PMRA No. 2502260	**BChE:** **PND18: BMD_{10} = 0.018/0.014 ♂/♀; $BMDL_{10}$ = 0.002/0.001 mg/kg bw/day ♂/♀** **PND48: BMD_{10} = 0.246/0.534 ♂/♀; $BMDL_{10}$ = 0.013/0.092 mg/kg bw/day ♂/♀** **Combining age groups:** BChE BMD/$BMDL_{10}$ = 0.062/0.011 mg/kg bw /day (♂); 0.12/0.028 mg/kg bw/day (♀) **EChE:** **PND18: BMD_{20} = 1.1/1.24 ♂/♀; $BMDL_{20}$ = 0.484/0.785 mg/kg bw/day ♂/♀** **PND48: BMD_{20} = 0.198/0.193 ♂/♀; $BMDL_{20}$ = 0.0187/0.121 mg/kg bw/day ♂/♀** **Combining age groups:** EChE BMD/$BMDL_{20}$ = 1.292/0.7 mg/kg bw /day (♂); ♀ EChE shows divergent response but in part of the dose response curve were there is no data; poor fit but not problematic as EChE is less sensitive than BChE (BChE is the driver) ≥0.1 mg/kg bw/day: ↓ BChE activity (PND 18 pups: ♂: 26%; ♀: 24%). ≥7.5 mg/kg bw/day: ↓ BChE activity (PNDs 18 and 48: range of 54-64%) and EChE activity (PNDs 18 and 48: range of 54-58%); tremors (1 ♂ on PND 48) (♂). 15 mg/kg bw per day: slight tremors (throughout study, PNDs 18 and 48), ↓ BChE activity (PNDs 18 and 48: range of 72-78%) and EChE activity (PNDs 18 and 48: range of 54-65%).

Study Type/ Animal/ PMRA #	Study Results
90-Day Neurotoxicity, Oral (gavage) Rat, Strain - N/S PMRA Nos. 2541047, 2541048, 2541049, 2541050	**NOAEL = 0.1 mg/kg bw/day** ≥7.5 mg/kg bw/day: ↑ tremors, salivation, exophthalmos, lacrimation (15 mins post-dosing, starting from the 1^{st} wk), ↓ PChE, EChE and BChE activity. 15 mg/kg bw/day: clear material on forelimbs, rales, chromodacryorrhea and material around the mouth; ↓ bw (♀). **No neuropathology or FOB effects.**
Acute Delayed Neurotoxicity, Oral (gavage) Hen, White Leghorn Given second dose at day 22, observed until day 42	16.5 mg/kg bw: lethargy, depression, incoordination, limb weakness, wing drop and ↓ reaction to external simulation (asymptomatic by day 3), peripheral nerve lesions associated with paralysis (degeneration in the proximal right sciatic nerve with axonal swelling in proximal and distal parts of nerve (1/10 hens)). **Equivocal for acute delayed neurotoxicity.**
28-Day Delayed Neurotoxicity, Oral (gavage) Hen, Ross Hi-Sex Brown Observed for 47 or 77 days after onset of dosing	0.3 mg/kg bw/day: axonal degeneration (cerebellum, sciatic nerve, spinal cord and tibial nerve), histopathology (splitting/thickened and/or densely staining material within myelin), ↓ BChE activity (day 30) 1.0 mg/kg bw/day: ↑ mortality (1/21 hens), unsteady gait, inability to stand (2/21 hens), ↓ BChE activity (days 4 and 30). 3.0 mg/kg bw/day: ↑ mortality (4/21 hens), outstretched wings, birds being pecked, limping, inability to stand, quiet/subdued, unsteadiness, ↓ BChE activity (days 4 and 30). Brain and spinal cord NTE not affected. Note: EPL Pathology Working Group states that study is negative for OPIDN. However, there are inconsistencies between EPL report and other reviews of the original study. **Considered equivocal for evidence of delayed neurotoxicity. Issues remain concerning discrepancies between EPL report on this study and other study reviews.**
Range-finding Developmental Neurotoxicity Study, Oral (gavage) **Rat, Wistar (pregnant ♀)** **Dams exposed from GD 7 to LD 22**, BChE and EChE activity measured in dams on GD 22 and LD 22 and in the	**Maternal** No treatment-related effect on the number of mortalities, clinical signs, gestation length, number of live pups at birth or litter size. 0.1 mg/kg bw/day: 1 whole litter loss. 1 mg/kg bw/day: 1 whole litter loss, significantly ↓ BChE activity (LD 22: 12%) and EChE activity (GD 22: 25%, LD 22: 18%). 7.5 mg/kg bw/day: 2 whole litter losses, slightly ↓ bw, irregular breathing (1 dam, 3 consecutive days), significantly ↓ BChE activity

Study Type/ Animal/ PMRA #	Study Results
fetuses on GD 22 and in pups on PNDs 2, 8, 15, and 22 **PMRA Nos.** 2480293 and 2489911	(GD 22: 59%, LD 22: 67%) and EChE activity (GD 22: 52%, LD 22: 46%). **Offspring** No treatment-related clinical signs. 1 mg/kg bw/day: ↑ proportion of ♂ pups (65% compared to 51% in controls, no dose-response); significantly ↓ mean bw (5.8%) (♂). 7.5 mg/kg bw/day: ↑ incidence of 'cold' pups (PNDs 1 and 2); significantly ↓ mean bw (7.2%) (♂). **Fetuses** 7.5 mg/kg bw/day: significantly ↓ BChE activity (GD 22: ♂: 16%; ♀: 21%) and EChE activity (GD 22: ♂: 18%; ♀: 21%).
Developmental Neurotoxicity Study, Oral (gavage) **Rat, Wistar** **Dams exposed from GD7 to LD7, offspring dosed from PNDs 8 to 22** **PMRA Nos.** 2480293 and 2489911	**Maternal** 7.5 mg/kg bw/day: clinical signs (LD3, 1 dam), ↓ number of available litters (14 compared to ≥ 21 in other groups). **Offspring** 1.0 mg/kg bw/day: ↓ % of successful trials relative to the straight swim channel time (PND 62) (♂). 7.5 mg/kg bw/day: ↑ hippocampus width (level 5, PND63), ↑ dentate gyrus width (Levels 4 and 5, PND 63), ↑ piriform cortex thickness (♂: Level 5; ♀: Level 4); ↑ mean maximum amplitude of auditory startle response (PND 23, equivocal at 0.1 and 1.0 mg/kg bw/day), ↓ % of successful trials relative to straight swim channel time (PND 27), ↓ thickness of inner granular layer of the prepyramidal fissure (PND 63), ↓ thalamus height (Level 4, PND 63) (♂); ↓ % of successful trials relative to straight swim channel time (PNDs 27 and 62) (♀). Note: No brain morphometric measurements were taken for the low- and mid-dose animals **Supplemental due to high pup mortality from LDs 1-5 (22.6%, 17.4%, 17.5% and 28.1% at 0, 0.1, 1.0 and 7.5 mg/kg bw/day, respectively) and total litter loss (20.0%, 10.0%, 17.9% and 18.5% at 0, 0.1, 1.0 and 7.5 mg/kg bw/day, respectively), low confidence in FOB parameters due to the lack of specificity in parameter gradation criterion and low confidence in motor activity results due to lack of habituation in all groups including control at both PNDs 22 and 60.**
Supplementary Developmental Neurotoxicity Study, Oral (gavage)	**Maternal** 7.5 mg/kg bw/day: ↑ incidence of salivation (2 dams). **Offspring** 7.5 mg/kg bw/day: slight ↑ mean maximum amplitude of the auditory

Study Type/ Animal/ PMRA #	Study Results
Rat, Wistar **Dams exposed from GD7 to LD7, offspring dosed from PNDs 8 to 22** **PMRA Nos.** 2480293 and 2489911	startle response on PND 23 (♂); ↑ absolute cerebellum wt (PND 12: 14%) (♀). **Supplemental due to high pup mortality from LDs 1 to 5 and total litter loss at 0 and 7.5 mg/kg bw/day, respectively, low confidence in FOB parameters due to the lack of specificity in parameter gradation criterion and low confidence in motor activity results due to lack of habituation in control and treated groups at both PNDs 22 and 60.**
Special Studies (non-guideline, all considered supplemental for risk assessment purposes)	
Reproductive Function, Oral (gavage) Mouse, NMRI (♂)	i) 40 mg/kg bw (single dose). ii) 10 mg/kg bw/day, daily for 18 days. ≥10 mg/kg bw/day: ↓ testicular wt, damaged seminiferous tubules (desquamation, ↓ cell population, "holes"), damage to supporting Sertoli cells, ↓ number of Sertoli cells, ↑ number and hypertrophy of Leydig cells. Severe disturbances of spermatogenesis in both dichlorvos treated groups. Note: Histological examination of testes on days 9, 18, 27, 36, 54 and 63.
Reproductive Function, Oral (gavage) Rat, Wistar (♂)	i) 10 mg/kg bw/day, from PNDs 4 to 23. 10 mg/kg bw/day: slightly ↓ number of spermatogenic and Leydig cells (changes reversed by PND 50). Note: Histological examination of testes on days 6, 12, 18, 26, 34 and 50.
Reproductive Function, Oral (gavage) Rat, Wistar (♂)	i) 10 mg/kg bw/day, on alternate days for 2 wks ii) 5 mg/kg bw/day, on alternate days for 3 wks ≥5 mg/kg bw/day: ↑ seminal vesicle wt. Note: Measured serum FSH, LH, testosterone, testes and seminal vesicles weighed and examined histologically.
In utero exposure and brain function (non-guideline), Oral (gavage) Rat, Wistar	**12-wk old rats** ≥0.97 mg/kg bw/day: dose-dependent ↓ mean spontaneous EEG amplitudes at all three cortical sites - somatosensory, visual, auditory, ↓ EEG index, dose-dependent ↑ mean EEG frequencies at all three cortical sites - somatosensory, visual, auditory. 3.88 mg/kg bw/day: ↓ BChE activity (somatosensory visual and audio cortex).

Study Type/ Animal/ PMRA #	Study Results
	Note: Offspring anesthetized at 10 wks of age, electrode placed on the dura of the primary somatosensory, visual and audiocortex. Freely moving rats re-tested at 12 wks
In utero exposure and brain function (non-guideline), Oral (gavage) Rat, Wistar **Dams exposed from GD1 to LD21, offspring dosed from 6 wks of age**	**Offspring** ≥0.97 mg/kg bw/day: ↑ running time and incorrect choices in T-maze, ↑ horizontal activity, ↓ vertical activity, ↓ defecation, ↓ sleep scores in novelty-induced grooming test, ↓ BChE activity, ↓ blood serum AChE activity. Note: Daily T-maze tests from 9 to 12 wks, open-field test and novelty induced grooming test at 12 wks.
4-wk Reproductive Study (non-guideline), Oral (gavage) Rat, Wistar (♀) PMRA No. 2489925	4 mg/kg bw/day: ↓ bwg, severe muscle fasciculations, ↓ serum ChE activity, significantly ↓ number of estrus cycles with ↓ duration of each phase (other than diestrus that showed ↑ duration), significantly ↑ level of malondialdehyde, significant alterations of the endometrium (irregular epithelial lining, disorganization of the glandular epithelium, shrinkage of epithelial cells in the endometrial glands and pyknotic nucleus in epithelial cells), significantly ↑ caspase-3 expression in epithelial and stromal cells of endometrium. 4 mg/kg bw/day plus Vitamin C (50 mg/kg bw) and Vitamin E (20 mg/kg bw): similar effects as above but to a lesser degree. Vitamins C and E did not offer complete protection from dichlorvos-induced reproductive toxicity.
48-Day Reproductive Study (non-guideline), Oral (gavage) Rat, Wistar (♂) PMRA No. 2489909	10 mg/kg bw/day: significantly ↓ sperm motility of spermatozoa released from the cauda epididymis, ~65% of the spermatozoa residing in the lumen of the cauda epididymis retained the cytoplasmic droplet (versus 0% in controls).
4 and 7-wk Reproductive Study (non-guideline), Oral (gavage) Rat, Wistar (♂) PMRA No. 2489913	1.6 mg/kg bw/day: ↓ bw and testis wt (4 and 7 wks), ↓ total epididymal sperm motility (7 wks), ↑ level of abnormal sperm morphology (4 and 7 wks), ↓ FSH, LH and testosterone levels (4 and 7 wks), structural abnormalities in the epithelium of the seminiferous tubules (4 wks), edema in the interstitial tissue of the testes (7 wks), necrosis in seminiferous tubules (7 wks), morphological abnormalities in spermatozoa, dense swellings and vacuolization in the mitochondria of Sertoli cells (4 and 7 wks), ↑ in lysosomal structures and severe morphological abnormalities in spermatozoa (7 wks) 1.6 mg/kg bw/day plus Vitamin C (200 mg/kg bw) and Vitamin E (200 mg/kg bw): similar effects as above but to a lesser degree. Vitamins C and E did not offer complete protection from dichlorvos-induced reproductive toxicity.

Study Type/ Animal/ PMRA #	Study Results
8-wk Reproductive Study (non-guideline), Oral (dietary) Rat, Lewis (♂) PMRA No. 2489927	2.3 mg/kg bw/day: slightly ↑ sperm transit time in the caput/corpus epididymis (22.2%), slightly ↓ number of spermatids (12.5%), ↓ daily sperm production (12.5%) and number of sperm in the cauda epididymis (20.2%), ↑ testosterone levels (71.7%) and ↓ LH (54.6%) levels. Exposure to dichlorvos did not alter on the % of normal shaped sperm or the level of FSH.
9-wk Reproductive Study (non-guideline), Oral (gavage) Rat, Wistar (♂) PMRA No. 2489924	≥5 mg/kg bw/day: ↓ EChE activity, ↓ sperm motility, ↓ relative heart wt, ↑ concentration of urinary metabolite dimethyl phosphate 10 mg/kg bw/day: ↑ limb tremors, ↓ testicular AChE and plasma BuChE activity, ↓ bw, ↓ heart and prostate wt, ↑ relative testis and adrenal gland wt, ↑ % of broken sperm and cytoplasmic droplets, ↑ cytoplasmic vacuolation and nuclear shrinkage in the epithelial cells of the ductus epididymis, ↓ ratio of ATP to ADP concentration in sperm at 60 mins, slightly ↑ plasma testosterone levels There were no treatment-related effects on the wt of the prostate, seminal vesicles, testes or epididymis or on histopathology of the testes.
Prenatal Neurotoxicity Study (non-guideline), **Oral (gavage)** **Rat, Wistar (pregnant ♀)** Dams exposed from GDs 6 to 15 Parameters assessed in ♂ and ♀ offspring and ♂ offspring raised to adulthood (age N/S) PMRA No. 2489916	**Maternal** 8 mg/kg bw/day: slightly ↓ bwg (GDs 6-15, ~5%). **Offspring** 8 mg/kg bw/day: ↑ immobility time in PND 21 pups; ↓ locomotor activity and rearing frequency in PND 21 pups, ↑ immobility time and ↓ locomotor frequency in offspring raised to adulthood, ↓ in latency to cross in the passive avoidance test in adults (52.7%) (♂). Stereotypy behavior induced by 0.6 mg/kg bw apomorphine was ↓ in the dichlorvos-exposed adult animals at 60 and 120 mins.
Placental Transfer (non-guideline), Oral (gavage) Rabbit, Strain - N/S	**Mean dichlorvos concentrations in fetal blood (µmol/L):** 5 mins: 0.814 ± 0.090 10 mins: 4.072 ± 0.361 20 mins: 7.692 ± 0.583 30 mins: 5.429 ± 0.407 120 mins: 0.542 ± 0.113 Unchanged dichlorvos rapidly transported across placenta to fetal circulation.
Acute Neurophysiology, Oral (gavage) Rat	88 mg/kg bw: ↑ mortality, clinical signs of toxicity, ↓ BChE activity, ↓ tissue AChE, EEG alterations (↓ in all components of frequency band and amplitude, ↑ in mean frequency) and ECG alterations (↑ absolute refractory periods, ↓ heart rate and amplitude of Q wave), ↓ conduction velocity of tail nerve.

Study Type/ Animal/ PMRA #	Study Results
Acute Cholinesterase Inhibition, Oral (gavage) Rat	40 mg/kg bw: ↓ AChE activity in GI mucosa, ↓ HCl production in GI mucosa, ↓ histidine decarboxylase, ↓ PChE activity, ↓ ACP and ALP. 50 mg/kg bw: ↓ BChE activity, ↑ brain acetylcholine. Note: Data presented from a variety of studies.
Acute Cholinesterase Inhibition, Oral (gavage) Dog, Beagle PMRA No. 2573217	42 mg/kg bw: ↓ PChE (recovery by days 3 to 5) and EChE (recovery by day 21 to 28) activity.
1-Day Cholinesterase Inhibition, Oral (gavage) Rat, Wistar PMRA No. 2480297	≥8.0 mg/kg bw: ↓ brain ALP, ↓ BChE activity. 40 mg/kg bw: ↓ brain ACP.
8-day Cholinesterase Inhibition, Dermal Guinea Pig, "P"-strain	≥25 mg/kg bw/day: ↓ PChE and EChE activity.
10-day Acetylcholinesterase activity and 5-HT (5-hydroxytryptamine) Concentration Study, Oral (gavage) Rabbit (juvenile)	Measured AChE activity and 5-HT in specific areas of brain and spinal cord. 9 mg/kg bw/day: ↓ AChE activity, alterations in 5-HT concentrations.
14-Day Cholinesterase Inhibition, Oral (gavage) Rat, Wistar	≥1.6 mg/kg bw/day: ↓ brain ACP and BChE activity.
1-Month Cholinesterase Inhibition, Oral (gavage) Mouse, B6C3F1 PChE and EChE activity measured on days 10, 11, 25, 26, 32 and 33, ~3 hrs post-treatment	5 mg/kg bw/day: ↓ PChE activity (dose-dependent). No effect on EChE activity. Note: Timing of determination of enzyme activities might have underestimated ChE inhibition.
1-Month Cholinesterase Inhibition, Oral (gavage) Rat, F344 PChE and EChE activity	≥2 mg/kg bw/day: ↓ PChE activity. EChE activity comparable to controls.

Study Type/ Animal/ PMRA #	Study Results
measured on days 10, 11, 25, 26, 32 and 33, ~3 hrs post-treatment	Note: Timing of determination of enzyme activities might have underestimated ChE inhibition.
4-wk Oral (dietary) Pullets and Hens, White Leghorn	3.75 mg/kg bw/day: ↓ PChE activity.
90-day Cholinesterase Inhibition, Oral (gavage) Rat, Wistar PMRA No. 2480297	1.6 mg/kg bw/day: slightly ↓ BChE activity.
90-Day Neurophysiology, Oral (gavage) Rat	≤4 mg/kg bw/day: ↓ cerebral cortex ChE, ↓ white matter ChE, EEG alterations (↓ mean amplitude, ↑ mean frequency) and ECG alterations (↓ area under the T-wave, ↑ amplitude of muscle action potentials), ↓ in tail nerve conduction velocity and ↑ relative and absolute refractory periods.
117-day Cholinesterase Inhibition, Oral (40 doses, gavage) Rat, Wistar	3.52 mg/kg/72 hrs: ↓ BChE activity (cortex, medulla, hypothalamus), ↓ muscle and liver AChE activity, hyperaemia in myocardium and in liver, extravasations in myocardium, necrobiosis in myocardium, vacuolar degeneration in liver. Note: Due to dosing regimen only considered qualitatively.
117-day Cholinesterase Inhibition, Dermal (40 doses) Rat	2.94 mg/kg bw/72 hrs: ↓ BChE activity. Note: Due to dosing regime and lack of detail, study only considered qualitatively.
6-wk Immune Function, Oral (gavage) Rabbit PMRA Nos. 2573208 and 2573218	≥0.62 mg/kg bw/day: ↓ EChE activity (starting from the first wk). 2.5 mg/kg bw/day: dose-related ↓ in immune function (significant suppression of humoral immune response (↓ serum antibody titer), significant suppression of cell-mediated immunity (tuberculin skin test)).
3-Month Electron Microscopy, Oral i) Rabbit ii) Monkey, Rhesus Examined external ocular muscle, liver, kidney, intercostal muscles and sacral nerves	i) ≤5.0 mg/kg bw/day; ii) ≤1.0 mg/kg bw/day Changes in neuromuscular junction (↓ in synaptic vesicles and disarrangement of the myofilaments), mitochondria (swelling and disordering of cristae with sparsely distributed atrophy), liver (binuclear cells, vacuolization of hepatocytes, ↑ SER and RER, ↓ glycogen granules, ↓ and flattening of villi in biliary canaliculi, Kupffer's cells swollen with numerous phagocytic granules) and muscle (↑ myelin bodies and atrophy of muscle fibres).

Study Type/ Animal/ PMRA #	Study Results
90-day Inhalation (vapour, continuous exposure) Monkey, Rhesus	0.00005 mg/L (~0.020 mg/kg bw/day): ↓ PChE and EChE activity. No effect on nerve conduction or muscle-evoked action potentials. ChE measured monthly.
4-wk Hepatotoxicity Study, Oral (drinking water) Rat, Sprague-Dawley (♂) PMRA No. 2489912	≥0.6 mg/kg bw/day: ↓ bw (14.4%), ↑ AST, ALT, LDH, ALP and WBC levels. 1.2 mg/kg bw/day: ↓ bw (13.4%), ↑ MCH levels.
4 and 7-wk Hepatotoxicity Study, Oral (gavage) Rat, Wistar (♂) PMRA No. 2489923	1.6 mg/kg bw/day (in corn oil): ↓ bw and fc (4 and 7 wks), ↑ liver wt (4 and 7 wks), ↓ total protein, albumin, triglyceride, LDL cholesterol levels (4 and 7 wks), ↑ ALP, ALT, AST, GGT, LDH and total cholesterol levels (4 and 7 wks), dilatation of hepatocellular endoplasmic reticulum (4 wks), mitochondrial matrix and cristae were lost in hepatocytes (4 wks), swelling of the mitochondria, loss of cytoplasm and pyknotic nuclei in hepatocytes (7 wks). 1.6 mg/kg bw/day (in corn oil) plus Vitamin C (200 mg/kg bw/day) and Vitamin E (200 mg/kg bw/day): similar effects as above but to a lesser degree. Vitamins C and E ↓ dichlorvos hepatotoxicity but did not offer complete protection from dichlorvos-induced hepatotoxicity.
In vitro Estrogen and Androgen Activity Assays **Cell proliferation and Estrogen receptor transactivation assays - MCF-7 cells** **Androgen receptor transactivation - CHO K1 cells** **Aromatase activity - human placental microsomes** PMRA No. 2489910	**Cell proliferation**: no treatment-related effect in this assay, cytotoxicity noted at >50 μmol/L. **Estrogen receptor transactivation**: no treatment-related effect in this assay, cytotoxicity noted at >50 μmol/L. **Androgen receptor transactivation**: 20 μM: dichlorvos acted as a very weak antiandrogen reducing the response of the synthetic androgen R1881 by 78%, cytotoxicity noted at >100 μmol/L. **Aromatase activity:** no treatment-related effect in this assay.
In vivo Unscheduled DNA Synthesis, **Replicative** DNA Synthesis **and assessment of forestomach epithelium** **Mouse, B6C3F1 (♂)**	10 mg/kg bw: ↑ incidence of focal cell hypertrophy (2♂, 2♀) and focal hyperplasia (1♂, 1♀) of forestomach epithelium; ↑ proportion of forestomach epithelial cells in S-phase (♂); ↑ mortality (1♀). 20 mg/kg bw: ↑ incidence of focal (2♂, 2♀) and diffuse (2♂, 1♀) cell hypertrophy and focal hyperplasia (3♂, 3♀) of forestomach epithelium;

Study Type/ Animal/ PMRA #	Study Results
Positive controls: MNNG (genotoxic forestomach carcinogen) and BHA (irritant, non-genotoxic forestomach carcinogen) **PMRA No. 2534673**	↑ proportion of forestomach epithelial cells in S-phase, ↑ incidence of diffuse hyperplasia (1♀) of forestomach epithelium (♀). 40 mg/kg bw: ↑ mortalities (1♂, 1♀), ↑ incidence of focal (1♂, 3♀) and diffuse (4♂, 2♀) cell hypertrophy and focal hyperplasia (5♂, 4♀) of forestomach epithelium; ↑ proportion of forestomach epithelial cells in S-phase (♂); ↑ incidence of diffuse hyperplasia (1♀) of forestomach epithelium (♀). 100 mg/kg bw: ↑ incidence of diffuse cell hypertrophy (3♂, 5♀) of forestomach epithelium; ↑ mortalities (4♂), ↑ incidence of focal cell hypertrophy (1♂) and focal hyperplasia (5♂) of forestomach epithelium (♂); ↑ proportion of forestomach epithelial cells in S-phase (♀), ↑ incidence of diffuse hyperplasia (5♀) of forestomach epithelium (♀). MNNG: ↑ mortalities (1♂, 1♀), ↑ mean number of grains per nucleus and % of cells in repair (maximal response noted at 4 hrs, greater in ♂s than ♀s), ↑ incidence of diffuse cell hypertrophy (4♂, 5♀) of forestomach epithelium; ↑ proportion of forestomach epithelial cells in S-phase (♂). BHA: ↑ proportion of forestomach epithelial cells in S-phase, ↑ incidence of diffuse cell hypertrophy (5♂, 4♀) and diffuse hyperplasia (4♂, 5♀) of forestomach epithelium; ↑ incidence of focal hyperplasia of forestomach epithelium (1♂); ↑ incidence of focal cell hypertrophy of forestomach epithelium (1♀). Under the conditions of this assay, dichlorvos did not induce UDS while it induced RDS and hyperplasia in the forestomach epithelium, similar to the positive control BHA. MNNG induced UDS, RDS and hypertrophy of the forestomach epithelium but hyperplasia was not noted in this group.
Metabolite Toxicity Studies	
Dichloroacetaldehyde (DCA) 1-Month Inhalation Study Rat	0.5-1 mg/m^3: minor inflammatory changes in lungs, slightly ↓ bw, slightly ↓ fc, slightly ↑ liver wt (♂) in animals sacrificed at day 30, no changes seen in animals sacrificed at day 35.
Dichloroacetaldehyde (DCA) and 2,2-dichlorethanol Mutagenicity Study *S. typhimurium*, TA100	**i) Dichloroacetaldehyde (DCA)**: Positive. Mutagenicity ↓ in the presence of microsomal activation system, partly dependent on presence of cofactors NADP and glucose-6-phosphate. **ii) 2,2-dichlorethanol**: Negative.

Study Type/ Animal/ PMRA #	Study Results
Dichloroacetaldehyde (DCA) Dominant Lethal Assay AB Jena-Halle strain and DBA strain Mice (♂)	i) AB Jena-Halle strain: ↓ total implants and live fetuses during first 3 wks, ↑ post-implantation loss ii) DBA strain: same effects as above but to a lesser degree and mostly seen during wk 4.

Table 2 Toxicology Reference Values for Use in Health Risk Assessment for Dichlorvos

Exposure Scenario	Endpoint	Study	CAF[a] or Target MOE
Acute Dietary (all populations)	BMDL$_{10}$ = 1.4 mg/kg bw (BChE inhibition)	Two Acute Oral ChE Inhibition Studies - neonate and young adult Rats	100
	ARfD = 0.014 mg/kg bw		
Chronic Dietary (all populations)	BMDL$_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	100
	ADI = 0.0001 mg/kg bw/day		
Dermal[b] Short-, Intermediate- and Long-term	BMDL$_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	100
Inhalation[c] Short-, Intermediate- and Long-term	BMDL$_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	100
Incidental Oral, Short-term	BMDL$_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	100
Aggregate Short-, Intermediate- and Long-term, Oral, Dermal[b] and Inhalation[c]	BMDL$_{10}$ = 0.011 mg/kg bw (BChE inhibition)	7-day Repeat-dose Oral ChE Inhibition Study - PND 18 and 48 rats	100
Cancer Oral, Dermal and Inhalation	Dichlorvos is an in vitro mutagen and clastogen; however, the overall weight of evidence suggested that it is neither mutagenic nor clastogenic in vivo. The available evidence is insufficient to rule out the possibility that dichlorvos may be carcinogenic. Although available cancer studies have limitations, there is a large margin (~40,000) between the proposed reference values for repeat-exposure and the lowest dose resulting in tumours in the available dichlorvos studies.		

[a] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments.

[b] Since an oral NOAEL was selected, a 30% dermal absorption factor was used for route-to-route extrapolation

[c] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used for route-to-route extrapolation

Appendix III

Table 1 Dietary Exposure and Risk Estimates for Dichlorvos

Population Subgroup	Refined							
	Acute Dietary (99.9th percentile)[1]				Chronic Dietary[2]			
	Food Only		Food + Water		Food Only		Food + Water	
	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ADI	Exposure (mg/kg/day)	%ADI
General Population	0.000294	2	0.000389	3	0.000009	9	0.000009	9
All Infants (<1 year old)	0.000470	3	**0.000720**	**5**	0.000007	7	0.000008	8
Children 1-2 years old	**0.000563**	**4**	**0.000630**	**5**	**0.000024**	**24**	**0.000024**	**24**
Children 3-5 years old	0.000411	3	0.000459	3	0.000019	19	0.000019	19
Children 6-12 years old	0.000190	1	0.000290	2	0.000011	11	0.000011	12
Youth 13-19 years old	0.000142	1	0.000222	2	0.000007	7	0.000007	7
Adults 20-49 years old	0.000181	1	0.000267	2	0.000008	8	0.000009	9
Adults 50-99 years old	0.000298	2	0.000345	3	0.000008	8	0.000008	8
Females 13-49 years old	0.000180	1	0.000264	2	0.000007	7	0.000007	8

[1] Acute Reference Dose (ARfD) of 0.014 mg/kg bw applies to the general population and all population subgroups;

[2] Acceptable Daily Intake (ADI) of 0.0001 mg/kg bw/day applies to the general population and all population subgroups.

Table 2 Dietary Exposure and Risk Estimates for Naled

Population Subgroup	Refined			
	Acute Dietary (99.9th percentile)[1]		Chronic Dietary[2]	
	Food + Water		Food + Water	
	Exposure (mg/kg bw/day)	%ARfD	Exposure (mg/kg bw/day)	%ADI
General Population	0.008321	14	0.000015	< 1
All Infants (<1 year old)	**0.021893**	**36**	**0.000033**	**2**
Children 1-2 years old	0.010507	18	**0.000032**	**2**
Children	0.008265	14	0.000029	1

Population Subgroup	Refined			
	Acute Dietary (99.9th percentile)[1]		Chronic Dietary[2]	
	Food + Water		Food + Water	
	Exposure (mg/kg bw/day)	%ARfD	Exposure (mg/kg bw/day)	%ADI
3-5 years old				
Children 6-12 years old	0.006938	12	0.000017	< 1
Youth 13-19 years old	0.006088	10	0.000012	< 1
Adults 20-49 years old	0.006847	11	0.000014	< 1
Adults 50-99 years old	0.006008	10	0.000011	< 1
Females 13-49 years old	0.006730	11	0.000012	< 1

[1] Acute Reference Dose (ARfD) of 0.06 mg/kg bw applies to the general population and all population subgroups;

[2] Acceptable Daily Intake (ADI) of 0.002 mg/kg bw/day applies to the general population and all population subgroups.

Table 3 ARI's for Combined Dietary Risk from Dichlorvos and Naled

Population Subgroup	ARI = 1 / (% $\mathrm{RfD}_{\mathrm{dichlorvos}}$ + % $\mathrm{RfD}_{\mathrm{naled}}$)[1]	
	Acute Dietary (99.9th percentile)	Chronic Dietary
	Food + Water	Food + Water
General Population	6	10
All Infants (<1 year old)	**2**	10
Children 1-2 years old	5	**4**
Children 3-5 years old	6	5
Children 6-12 years old	7	8
Youth 13-19 years old	9	13
Adults 20-49 years old	8	11
Adults 50-99 years old	8	11
Females 13-49 years old	8	12

[1] The combined risk was calculated using the aggregate risk index (ARI) methodology:

ARI = 1 / (% $\mathrm{RfD}_{\mathrm{dichlorvos}}$ + % $\mathrm{RfD}_{\mathrm{naled}}$)

$\% \text{ RfD}_{dichlorvos}$ and $\% \text{ RfD}_{naled}$ are the calculated risks from exposure to dichlorvos (Appendix III, Table 1) and naled (Appendix III, Table 2), respectively.

As a general rule, an ARI greater than or equal to 1 is not of concern, but an ARI less than 1 would require mitigation. The ARIs for the dietary exposure (from food and drinking water) to both naled and dichlorvos are all greater than 1 for both acute and chronic exposures and are, therefore, not of concern.

Appendix IV Food Residue Chemistry Summary

The current residue definition (RD) for dichlorvos is dichlorvos *per se* for both enforcement and risk assessment purposes. No change to the RD for enforcement purposes is being proposed. However, dichlorvos is also a metabolite and degradation product of naled which is currently a registered pesticide. Since dichlorvos residues from dichlorvos use cannot be distinguished from dichlorvos residues from naled use, the dichlorvos dietary risk assessment considered exposure from all pesticide sources. Dichlorvos is also a metabolite and degradation product of trichlorfon. However, all uses of trichlorfon in Canada have been discontinued and there are no registered food/feed uses in the US. Trichlorfon has veterinary uses on cattle in other countries; however, the degree of Canadian imports of cattle meat and meat byproducts from non-US countries is low.

The residue chemistry database for dichlorvos is incomplete for the currently registered use pattern. The registrant will be requested to provide the full data package compliant with residue chemistry guidelines (Dir98-02) for representative crops of vegetables registered on the label for greenhouse use and for postharvest treatment in warehouses and food handling establishments. The data will be required as part of any future submission concerning dichlorvos.

The currently registered product labels permit the use of the insecticide dichlorvos on greenhouse cucumbers and greenhouse tomatoes as well as in food manufacturing/processing facilities, livestock premises and warehouses containing bulk-stored and packaged or bagged non-perishable processed and raw foods. Products previously registered for direct animal application (livestock spray) under Pest Control Product Numbers 17422 and 28782 and for mushroom house use (Pest Control Product Number 11819) have been discontinued or are no longer supported by end use product manufacturers.

Canadian maximum residue limits (MRLs) have been established for residues of dichlorvos *per se* at 2 ppm in/on non-perishable packaged foods of high fat content (over 6%); at 0.5 ppm in/on non-perishable packaged foods of low fat content (under 6%); at 0.25 ppm in/on tomatoes; at 0.1 ppm in fat, meat and meat byproducts of hogs; at 0.05 ppm in fat, meat and meat byproducts of poultry; and at 0.02 in milk and fat, meat, and meat byproducts of cattle and horses. These MRLs are published on Health Canada's Maximum Residue Limits for Pesticides webpage. No MRL has been specified for cucumber and mushroom (import); dichlorvos residues in/on cucumber and mushroom are, therefore, regulated under the General MRL not to exceed 0.1 ppm.

Dichlorvos is currently registered in the US for the same uses as in Canada except uses on greenhouse cucumber and greenhouse tomato. There are no agricultural crop uses of dichlorvos in the US. Established US tolerances for dichlorvos are aligned with Canadian MRLs. Codex MRLs are established for dichlorvos residues at the limit of determination (0.01 ppm) in all commodities of animal origin. Codex MRLs are also established in rice and wheat and processed fractions thereof, and spices. The Codex residue definition for enforcement is the same as the one used in Canada and US (*that is,* dichlorvos *per se*). Dichlorvos (like naled)) is not authorized for use in European countries.

Dichlorvos residues from the most recent (2008-2014) CFIA and PDP residue monitoring data were generally non-detects. For a few exceptions (almonds, cucumbers, peppers and strawberries), the detected residues were below the established MRLs and most of them were close to the limits of detection.

Appendix V Non-Occupational Risk Assessment

Table 1 Postapplication Inhalation Exposure and Risk Assessment for Pest Strips

Scenario	AC[A] (mg/m^3)	IR (m^3/hr)	ET[B] (hr/day)	Inhalation Exposure[C] (mg/kg bw /day)	Inhalation MOE[D] (Target = 100)
Exposure from Areas Occupied for up to 4 hours per Day (for example, attics, garages, etc.)					
Adult	0.035	0.64	4	1.10×10^{-3}	**10**
Youth (aged 6 to < 11 years)		0.63		1.53×10^{-3}	**7**
Children (aged 3 to < 6 years)		0.42		3.05×10^{-3}	**4**
Children (aged 1 to < 2 years)		0.33		4.14×10^{-3}	**3**
Exposure from Areas Adjacent to an Area with Pest Strip					
Adult	0.004	0.64	10	3.13×10^{-4}	**35**
Youth (aged 6 to < 11 years)		0.63	11	4.94×10^{-4}	**22**
Children (aged 3 to < 6 years)		0.42	12	1.04×10^{-3}	**11**
Children (aged 1 to < 2 years)		0.33	13	1.58×10^{-3}	**7**

IR = Inhalation Rate, MOE = Margin of Exposure, BW = Body Weight

[A] AC = Air Concentration. Air concentration value was calculated based on a registrant submitted study (PMRA No. 2586571). A time-weighted average (TWA) value from the closet data (closet contained pest strip) was used to represent exposure from areas that could be occupied for up to 4 hours per day, such as, attics and garages. The TWA of air concentrations from the room adjacent to the closet was used to represent potential exposures to a room adjacent to an attic or crawl space that contains the pest strip.

[B] Exposure Time. A value of 4 hours was chosen based on label statement indicating the use in areas occupied for less than 4 hours/day . Exposure times for exposure from areas adjacent to an area where a pest strip is used in based on the amount of time spent in bedrooms from the USEPA Exposure Factors Handbook (USEPA, 2011). Bedroom was chosen to represent a worst-case scenario.

[C] Inhalation Exposure (mg/kg bw/day) = Air concentration (mg/m^3) × IR (m^3/hour) × ET (hr/day) × 1/BW where body weight (80 kg for adults, 57 kg for youth (11 < 16 years old), 19 kg for children 3 < 6 years old) and 11 kg for children (1 < 2 years old)

[D] Adult, youth and children long-term MOEs are based on an oral NOAEL of 0.011 mg/kg bw/day with a target MOE of 100

Table 2 Postapplication Inhalation Exposure and Risk Assessment for Outdoor Mosquito Control in Residential Areas

Scenario	IR (m^3/hr)	Inhalation Exposure[A] (mg/kg bw /day)	Inhalation MOE[B] (Target = 100)
Outdoor Aerosol Space Spray			
Adult (80 kg)	0.64	0.039	**< 1**
Youth (aged 6 to < 11 years) (57 kg)	0.63	0.053	**< 1**
Children (aged 1 to < 2 years) (11 kg)	0.33	0.144	**< 1**
Outdoor Residential Misting Systems			
Adult (80 kg)	0.64	0.002	**7**
Youth (aged 6 to < 11 years) (57 kg)	0.63	0.002	**8**
Children (aged 1 to < 2 years) (11 kg)	0.33	0.006	**2**

IR = Inhalation Rate, MOE = Margin of Exposure, BW = Body Weight, AR = Application Rate.

[A] Inhalation exposure calculated based on algorithms from the USEPA Residential SOPs (2012). For outdoor aerosol space sprays: Inhalation Exposure (mg/kg bw/day) = AR (26.31 g a.i./day) × IR (m^3/hour)/Q (5400 m^3/hour) × 1/BW

For outdoor residential misting systems:

Inhalation Exposure (mg/kg bw/day) = $\left(\frac{IR \times C_0 . V}{Q} \text{ int}(ET . PR) + \frac{(1 - R^{\text{frac}(ET.PR)}}{(1 - R)} \right)$

Where C_0 is the initial concentration calculated above, V is the volume of treated space of 90.6 m^3, Q is the airflow through the treated area value of 5400 m^3/hour, ET is exposure time in hr/day of 2.3, 1.9, and 2.3 for adults, youth, and children respectively, PR is the pulse rate of 1 spray event/hr, and T_{BA} is the time between application events (that is, the inverse of the pulse rate, or 1/PR).

[B] Adult, youth and children short-term MOEs are based on an oral NOAEL of 0.011 mg/kg bw/day with a target MOE of 100.

Table 3 Postapplication Inhalation Exposure and Risk Assessment for Theaters and Animal Barns

Scenario	AC[A] (mg/m³)	IR (m³/hr)	ET[B] (hr/day)	Inhalation Exposure[C] (mg/kg bw /day)	Inhalation MOE[D] (Target = 100)
Theaters (33 mg/m³)					
Adult (80 kg)	0.00086	0.64	3	2.05×10^{-5}	540
Youth (aged 6 to < 11 years) (57 kg)		0.63		2.84×10^{-5}	390
Children (aged 3 to < 6 years) (19 kg)		0.42		5.68×10^{-5}	200
Children (aged 1 to < 2 years) (11 kg)		0.33		7.70×10^{-5}	140
Animal Barns (17.4 mg/m³)					
Adult (80 kg)	0.00045	0.64	4	1.44×10^{-5}	762
Children (aged 3 to <6 years) (19 kg)		0.42	2	1.99×10^{-5}	551

IR = Inhalation Rate, AC = Air Concentration, MOE = Margin of Exposure, BW = Body Weight.

[A] Air concentration value was calculated based on a USEPA air model after 96 hours, reflective of a 4 day restricted-entry interval

[B] Exposure Time. A value of 3 hours was chosen for theaters to represent the longest duration for a theater visit. The exposure time for animal barns is from the USEPA Residential SOPs (2012).

[C] Inhalation Exposure (mg/kg bw/day) = Air concentration (mg/m³) × IR (m³/hour) × ET (hr/day) × 1/BW

[D] Adult, youth and children MOEs are based on an oral NOAEL of 0.011 mg/kg bw/day with a target MOE

Appendix VI Commercial Mixer/Loader/Applicator Risk Assessment

Table 1 Mixer/Loader/Applicator Exposure and Risk Assessment of Dichlorvos in Greenhouses

Crop	Application Equipment	Application rate	ATPD[A]	Amount handled per day (kg a.i./day)	Dermal Exposure[B] (mg/kg bw/day)	Inhalation Exposure[C] (mg/kg bw/day)	Dermal MOE[D]	Inhalation MOE[D]	Combined MOE[E]
Personal Protective Equipment: Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves and a respirator[F].									
Greenhouse cucumber, tomato, ornamentals	MPHW	0.00113 kg a.i./L	150 L/day	0.1695	4.67×10^{-4}	9.58×10^{-6}	20	1100	23
	Backpack	0.00113 kg a.i./L	150 L/day	0.1695	1.65×10^{-3}	1.32×10^{-5}	10	840	7
	MPHG	0.00113 kg a.i./L	3800 L/day	4.2940	3.95×10^{-2}	8.10×10^{-4}	< 1	14	< 1
	Automated Application	0.00005658 kg a.i./m^2	10000 m^2	0.5658	6.65×10^{-5}	4.46×10^{-7}	170	25000	170
Personal Protective Equipment: Chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves and a respirator[F].									
Greenhouse cucumber, tomato, ornamentals	MPHW	0.00113 kg a.i./L	150 L/day	0.1695	4.41×10^{-4}	9.58×10^{-6}	25	1100	24
	Backpack	0.00113 kg a.i./L	150 L/day	0.1695	1.29×10^{-3}	1.32×10^{-5}	8.5	840	8
	MPHG	0.00113 kg a.i./L	3800 L/day	4.2940	2.94×10^{-2}	8.10×10^{-4}	< 1	14	< 1

ATPD = area treated per day, MOE = margin of exposure, MPHW = manually pressurized handwand, MPHG = mechanically pressurized hand-gun

[A] The value for automated fogger is based on the use information received for dichlorvos for greenhouses. Other values are defaults based on the ATPD memo.

[B] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate × DA (30%))/80 kg body weight

[C] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight.

[D] Based on a short, intermediate and long-term oral NOAEL of 0.011 mg/kg bw/day, and a target MOE of 100 for the dermal endpoint and inhalation endpoint.

[E] Combined MOE = NOAEL (0.011 mg/kg bw/day, target MOE of 100)/(Dermal Exposure + Inhalation Exposure).

[F] 90% protection factor was used for the respirator.

Current PPE on the label states: Mid-level PPE + respirator. MOEs of concern (shaded) do not meet the target MOE even with the max-level PPE.

Table 2 Mixer/Loader/Applicator Exposure and Risk Assessment of Dichlorvos in Structures

Site	Application equipment	Max Application Rate (kg a.i./m^2 or m^3)	Area Treated Per Day (m^2 or m^3)[A]	Amount handled per day (kg a.i./day)	Dermal Exposure[B] (mg/kg bw/day)	Inhalation Exposure[C] (mg/kg bw/day)	Dermal MOE[D]	Inhalation MOE[D]	Combined MOE[E]	Restriction on Amount Handled (kg)
Personal Protective Equipment: Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, and a respirator[F].										
Tobacco Storage	Automated Fogger/ULV	0.000066	21000	1.39	1.63×10^{-4}	1.09×10^{-6}	68	10000	**68**	0.93
Dairies, piggeries, poultry houses, barns	Automated Fogger	0.0000174	610	0.01	1.25×10^{-6}	8.36×10^{-9}	8824	1300000	8741	0.93

Site	Application equipment	Max Application Rate (kg a.i./m^2 or m^3)	Area Treated Per Day (m^2 or m^3)^A	Amount handled per day (kg a.i./day)	Dermal Exposure^B (mg/kg bw/day)	Inhalation Exposure^C (mg/kg bw/day)	Dermal MOE^D	Inhalation MOE^D	Combined MOE^E	Restriction on Amount Handled (kg)
Sheds, stables, barns, loafing sheds, pigpens, outdoor areas, poultry houses	MPHW	0.00472	150	0.71	1.95×10^{-3}	4.00×10^{-5}	5.64	275	**5**	0.039
	Backpack	0.00472	150	0.71	6.89×10^{-3}	5.49×10^{-5}	1.60	200	**2**	0.011
	MPHG	0.00472	3800	17.92	1.65×10^{-1}	3.38×10^{-3}	0.07	3.25	**< 1**	0.012
Food processing plants, industrial plants, warehouses, theaters	Automated Fogger/ULV	0.0000330	350000	11.55	1.36×10^{-3}	9.10×10^{-6}	8.11	1209	**8**	0.93
Personal Protective Equipment: Chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, and a respirator^F.										
Tobacco Storage	Automated Fogger/ULV	0.000066	21000	1.39	1.33×10^{-4}	1.09×10^{-6}	83	10000	**82**	1.14
Sheds, stables, barns, loafing sheds, pigpens, outdoor areas, poultry houses	MPHW	0.00472	150	0.71	1.84×10^{-3}	4.00×10^{-5}	**6**	280	**6**	0.041
	Backpack	0.00472	150	0.71	5.38×10^{-3}	5.49×10^{-5}	**2**	200	**2**	0.014
	MPHG	0.00472	3800	17.92	1.23×10^{-1}	3.38×10^{-3}	**< 1**	**3.3**	**< 1**	0.016
Food processing plants, industrial plants, warehouses, theaters	Automated Fogger/ULV	0.0000330	350000	11.55	1.10×10^{-3}	9.10×10^{-6}	10	1200	**10**	1.14

ATPD = area treated per day, MOE = margin of exposure, MPHW = Manually pressurized handwand, MPHG = Mechanically pressurized hand-gun

[A] Volumes are based on the use information received for dichlorvos. Other values are defaults based on the ATPD memo.

[B] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate × DA (30%))/80 kg body weight

[C] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight.

[D] Based on a short, intermediate long-term oral NOAEL of 0.011 mg/kg bw/day, and a target MOE of 100 for the dermal endpoint and inhalation endpoint.

[E] Combined MOE = NOAEL (0.011 mg/kg bw/day, target MOE of 100)/ Dermal Exposure + Inhalation Exposure

[F] 90% protection factor was used for the respirator.

Table 3 Mixer/Loader/Applicator Exposure and Risk Assessment of Dichlorvos in Human Habitat and Residential Outdoors

Site	Application equipment	Max Application Rate (kg a.i./ha or kg a.i./L)^{A}	Area Treated Per Day^{B}	Amount handled per day (kg ai)	Dermal Exposure^{C} (mg/kg bw/day	Inhalation Exposure^{D} (mg/kg bw/day)	Dermal MOE^{E}	Inhalation MOE^{E}	Combined MOE^{F}
Personal Protective Equipment: Coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves and a respirator^{G}.									
Outdoor mosquito control	Automated Fogger	0.112	1200 ha	134.40	1.58×10^{-2}	1.06×10^{-4}	0.70	100	**< 1**
	Truck Mounted ULV	0.113	1200 ha	135.60	9.63×10^{-2}	1.65×10^{-3}	0.11	6.68	**< 1**
Outdoor living areas, picnic grounds, backyard areas, patios, latrines, loading docks, parking and refuse areas, and other areas around buildings	MPHW	0.00472	150 L	0.71	1.95×10^{-3}	4.00×10^{-5}	5.64	275	**5**
	Backpack	0.00472	150 L	0.71	6.90×10^{-3}	5.50×10^{-5}	1.60	200	**2**
	MPHG	0.00472	3800 L	17.94	1.65×10^{-1}	3.39×10^{-3}	0.07	3.25	**< 1**
Personal Protective Equipment: Chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves and a respirator^{G}.									
Outdoor mosquito control	Automated Fogger	0.112	1200 ha	134.40	6.67×10^{-2}	1.63×10^{-3}	0.17	6.74	**< 1**
	Truck Mounted ULV	0.113	1200 ha	135.60	6.73×10^{-2}	1.65×10^{-3}	0.16	6.68	**< 1**
Outdoor living areas, picnic grounds, backyard areas, pations, latrines, loading docks, parking and refuse areas, and other areas around buildings	MPHW	0.00472	150 L	0.71	1.84×10^{-3}	4.00×10^{-5}	5.97	275	**5.87**
	Backpack	0.00472	150 L	0.71	5.38×10^{-3}	5.50×10^{-5}	2.04	200	**1.98**
	MPHG	0.00472	3800 L	17.94	1.23×10^{-1}	3.39×10^{-3}	0.09	3.25	**< 1**
Personal Protective Equipment: Closed Cab, Chemical-resistant coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves and a respirator^{G}.									
Outdoor mosquito control	Truck Mounted ULV	0.113	1200 ha	135.60	1.96×10^{-2}	1.61×10^{-4}	0.56	68.31	**< 1**

ATPD = area treated per day, MOE = margin of exposure, MPHW = Manually pressurized handwand, MPHG = Mechanically pressurized hand-gun

[A] Application rates for outdoor living areas are expressed in units of kg a.i./L. Application rates for outdoor mosquito control are expressed in units of kg a.i./ha.

[B] Based on the PMRA Area Treated Per Day Memo.

[C] Dermal exposure (mg/kg bw/day) = (dermal unit exposure × ATPD × maximum application rate × DA (30%))/80 kg body weight

[D] Inhalation exposure (mg/kg bw/day) = (inhalation unit exposure × ATPD × maximum application rate)/80 kg body weight.

[E] Based on a short- and intermediate-term oral NOAEL of 0.011 mg/kg bw/day, and a target MOE of 100 for the dermal endpoint and inhalation endpoint.

[F] Combined MOE = NOAEL (0.011 mg/kg bw/day, target MOE of 100)/(Dermal Exposure + Inhalation Exposure)

[G] 90% protection factor was used for the respirator.

Appendix VII Postapplication Worker Risk Assessment

Table 1 Combined Postapplication Greenhouse Risk Assessment

Crop	Transfer Coefficient (cm^2/hr)	Target DFR (ng/cm^2)[A]	Dermal REI[B] (days)	Inhalation REI[C] (days)	Req REI[D] (days)	DFR on REI Day (ng/cm^2)[E]	AC on REI Day (mg/m^3)[F]	Dermal Exposure (mg/kg bw/day)[G]	Inhalation Exposure (mg/kg bw/day)[H]	Combined Exposure (mg/kg bw/day)[I]	Combined MOE[F] (Target = 100)[J]
Cut Flower Ornamentals	4000	0.92	20	4	20	0.94	4.45×10^{-13}	1.13×10^{-4}	4.45×10^{-17}	1.13×10^{-4}	**98**
Potted Greenhouse Ornamentals	230	15.94	3	4	4	8.24	6.40×10^{-1}	5.69×10^{-5}	6.40×10^{-5}	1.21×10^{-4}	**91**
Greenhouse Cucumbers, Tomatoes	1400	2.62	9	4	9	2.76	1.02×10^{-4}	1.16×10^{-4}	1.02×10^{-8}	1.16×10^{-4}	**95**

[A] Target DFR is the DFR value required to have worker exposure for a specific-crop activity combination reach the target MOE of 100. It is calculated using the following formula: Target DFR (ng/cm^2) = [NOAEL (11 µg/kg bw/day) * Body Weight (80 kg) * Conversion Factor (1000 ng/µg)] ÷ [TC (cm^2/hr) * Duration (8 hrs) * Target MOE (100) * Dermal Absorption (30% or 0.3)]

[B] Time to reach target DFR was calculated using the equation of the line of DFR (ng/cm^2) versus time (hrs) of $y = 3908.65x^{-1.35}$ (Manninen et al. 1996). Time (hrs) = $(\text{Target DFR } (ng/cm^2)/3908.65)^{-1/1.35}$

[C] Time required to reach the target air concentration using air concentration data from Manninen et al., 1996.

[D] The REI required to reach the target DFR or target air concentration.

[E] Dislodgeable foliar residue on the required REI day calculated using the DFR equation from Manninen et al. 1996, DFR (ng/cm^2) = $3908.65 (\text{time in hours})^{-1.35}$.

[F] Air Concentration on the DFR day calculated using the natural log transformed linear regression of air concentration data from greenhouse (50 mg/m^3) in Manninen et al., 1996, air concentration (mg/m^3) = $e^{-0.0729(\text{time in hours}) + 6.5515}$.

[G] Calculated using the following formula: Dermal Exposure (mg/kg bw/day) = [TC (cm^2/hr) × Duration (8 hours/day) × DFR (ng/cm^2) × Dermal Absorption (30%) × Conversion Factor (1.0×10^{-6} mg/ng)] ÷ Body Weight (80 kg)

[H] Calculated using the following formula: Inhalation Exposure (mg/kg bw/day) = [Air Concentration ($\mu g/m^3$) × Light Inhalation Rate (1 m^3/hr) × Duration (8 hrs/day) × Conversion Factor (0.001 mg/µg)] ÷ Body Weight (80 kg)

[I] Combined Exposure at required REI (mg/kg bw/day) = Dermal Exposure (mg/kg bw/day) + Inhalation Exposure (mg/kg bw/day)

[J] Margin of Exposure at required REI (target = 100), calculated using the following formula: MOE = NOAEL (oral value = 0.011 mg/kg bw/day) ÷ Combined Exposure (mg/kg bw/day).

Table 2 Postapplication Risk Assessment for Structural Sites based on the USEPA Model in Food Processing Plants

Time (hr)	Estimated Concentrations[A] (mg/m³)			Inhalation Exposure[B] (mg/kg bw/day)			Margin of Exposure[C]		
	Tobacco (66.0 mg/m³)	**Barn[D]** (17.4 mg/m³)	**Warehouse[E]** (33.0 mg/m³)	**Tobacco** (66.0 mg/m³)	**Barn[D]** (17.4 mg/m³)	**Warehouse[E]** (33.0 mg/m³)	**Tobacco** (66.0 mg/m³)	**Barn[D]** (17.4 mg/m³)	**Warehouse[E]** (33.0 mg/m³)
24	25.1	6.61	12.5	3.13×10^{-1}	8.26×10^{-2}	1.57×10^{-1}	**< 1**	**< 1**	**< 1**
48	1.79	4.71×10^{-1}	8.94×10^{-1}	2.24×10^{-2}	5.89×10^{-3}	1.12×10^{-2}	**< 1**	**2**	**1**
72	1.28×10^{-1}	3.36×10^{-2}	6.38×10^{-2}	1.60×10^{-3}	4.21×10^{-4}	7.98×10^{-4}	**7**	**26**	**14**
96	9.11×10^{-3}	2.40×10^{-3}	4.55×10^{-3}	1.14×10^{-4}	3.00×10^{-5}	5.69×10^{-5}	97	367	193

[*] Application rate in parenthesis.

[A] Estimated concentrations were based on the following equation: $C_o = {}^{12} I_{11} (C_i) * e^{-kt}$ where: C_o = Predicted air concentration (mg/m³), C_i = Initial air concentration, which is equal to the application rate, k = decay constant (0.11) (USEPA 2000a), t = time (hours) representing an 8 hour work period postapplication

[B] Inhalation Exposure (mg/kg bw/day) = Air concentration (mg/m³) × IR (1 m³/hour) × 1/BW body weight (80 kg for adult). Since the air model estimates the air concentration that a worker is exposed to over an 8 hour period, the exposure time was not considered in the equation.

[C] MOEs = NOAEL (oral value of 0.011 mg/kg bw/day) / Inhalation Exposure (mg/kg bw/day), Target MOE is 100.

[D] Includes dairies, piggeries, and poultry houses.

[E] Includes food processing plants, industrial plants, and theaters.

Appendix VIII Aggregate Risk Assessment

Table 1 Aggregate Risk Assessment for Theaters and Animal Barns

Scenario	Inhalation Exposure[A] (mg/kg bw/day)	Dietary Exposure[B] (mg/kg bw/day)	Aggregate Exposure[C] (mg/kg bw/day)	Aggregate MOE[D] (Target = 100)
Theaters (33 mg/m³)				
Adult (80 kg)	2.05×10^{-5}	8.00×10^{-6}	2.95×10^{-5}	385
Youth (aged 6 to < 11 years) (57 kg)	2.84×10^{-5}	1.30×10^{-5}	4.14×10^{-5}	266
Children (aged 3 to < 6 years) (19 kg)	5.68×10^{-5}	1.90×10^{-5}	7.58×10^{-5}	145
Children (aged 1 to < 2 years) (11 kg)	7.70×10^{-5}	2.40×10^{-5}	1.01×10^{-4}	109
Animal Barns (17.4 mg/m³)				
Adult (80 kg)	1.44×10^{-5}	8.00×10^{-6}	2.34×10^{-5}	490
Children (aged 3 to <6 years) (19 kg)	1.99×10^{-5}	1.90×10^{-5}	3.89×10^{-5}	282

[A] Inhalation Exposure. See Appendix VII, Table 3.

[B] Chronic dietary exposure values including drinking water. Dichlorvos exposure was estimated using residues of dichlorvos from all sources, that is, residues of dichlorvos from use of dichlorvos, as well as, residues of dichlorvos resulting from use of naled.

[C] Aggregate Exposure (mg/kg bw/day) = Inhalation Exposure (mg/kg bw/day) + Dietary Exposure (mg/kg bw/day)

[D] Adult, youth and children MOEs are based on an oral NOAEL of 0.011 mg/kg bw/day with a target MOE of 100

Appendix IX Environmental Assessment

Table 1 Physico-chemical Properties of Dichlorvos

Properties	**Value**	**Comments**
Water solubility	18,000 mg/L at 25C	Very soluble
Vapour pressure	1.2×10^{-2} mm Hg at 20°C (1.6 Pa) (PMRA 2480292) 2.1×10^{3} mPa at 25°C (1.575×10^{-2} mm Hg) (PMRA 2758506)	Intermediate to high volatility under field conditions
Henry's law constant (Calculated)	2.545×10^{-7} atm.m^3/mol (PMRA calculated) 2.54×10^{-7} atm.m^3/mol (PMRA 2758506) 5.01×10^{-8} atm.m^3/mol (PMRA 2480292)	
1/H	9.61×10^{4} (PMRA calculated)	Slightly volatile from water or moist soil
Octanol/water partition coefficient (Log K_{ow})	Log K_{ow} = 1.9, 1.42 (different studies)	Low potential for bioaccumulation
UV/visible absorption spectrum	Not expected to absorb at $\lambda > 250$ nm	not susceptible to direct photolysis

Table 2 Summary of Abiotic Transformation Processes of Dichlorvos

Process	**Transformation**	**Comments**	**Reference**
Hydrolysis	half -lives of 11.65, 5.19, 0.88 days at pH 5, 7, and 9 respectively, at 25°C. major transformation products (amount not given) - 2,2-dichloroacetic acid (DCA), 2,2-dichloroacetaldehyde (DAA), desmethyl dichlorvos, and glyoxylic acid. half-lives of <1 to 30 days 15-20°C, pH 4 to 9 The slower half-lives are associated with studies in the pH 9 range, and the faster half-lives are associated with studies in the pH 4 range. DT_{50}s of 5 to 10 days at 37°C, pH 2 major transformation product 2,2-dichloroacetaldehyde	An important route of transformation at environmentally relevant pHs	PMRA 2480292 PMRA 2758511 PMRA 2758506 PMRA 2758506

Process	Transformation	Comments	Reference
	(26% peak) half-life at 4.5°C: 8.13 days (pH 7 low aeration), 7.42 days (pH 8 low aeration), 5.08 days (pH 8 high aeration) half-life at 13.5°C: 6.92 days (pH 7.7 low aeration), 6.38 days (pH 8 low aeration), 3.88 days (pH 8 high aeration) Extrapolated half-life for 20°C of 6.2 days at pH 7.7		
Phototransformation - water	Half-life = 10.2 days. Major transformation products, day 15: 2,2-dichloroacetaldehyde (32.7%) and desmethyl dichlorvos (17.8%) indirect photolysis in the presence of sensitizers in water is possible	Transformation in irradiated samples was not significantly different from dark control and not likely to be due to photolysis. Therefore, direct photolysis not an important route of abiotic transformation. Indirect photolysis may occur.	PMRA 2758506 PMRA 2758511
Phototransformation - soil	Half-life = 15.5 hours, sandy loam, pH 7, transformation products: 2,2-dichloroacetic acid (26.6%) and 2,2-dichloroethanol (4.4%)	Transformation in irradiated samples was not significantly different from dark control and not likely due to photolysis. Not an important route of abiotic transformation.	PMRA 2758506
Phototransformation - air	Estimated half-life of <0.5 to 2 days Calculated half-life of 13-20 hours	Degraded by hydroxyl radicals produced by photochemical reactions.	PMRA 2758511 PMRA 2758506

Table 3 Summary of Biotic Transformation Processes of Dichlorvos

Process	**System**	**DT$_{50}$**	**Comments**	**Reference**
Aerobic Soil Biotransformation	Soils with pH 6.8 and 2.6% OC, and pH 5.2 and 0.6% OC, at 20-24°C.	1 and 16 hours, respectively	Differences in rates attributed to differences in soil pH. Important route of biotic transformation	PMRA 2758511
	Non-sterile and sterile soil perfusion systems (soil pH 6.2-7.4, temperature ~26°C).	3.9 days - non-sterile soil 10 days - sterile soil	May be important route of biotic transformation Estimated 70% of total degradation in the non-sterile system was due to hydrolysis	PMRA 2758511
	Two soils (silty clay pH 5.5, and sandy clay pH 6.9) at 10, 100 and 1000 mg/kg dichlorvos and 25°C.	Silty clay: 10,100, and 1000 mg/kg = 12.9, 18.5, and 19.3 days, respectively (average 16.9 days) Sandy clay: 10, 100, and 1000 mg/kg = 12.3, 17.8, 18.2 days, respectively (average 16.1 days) no clear difference between the soils	Important route of biotic transformation	PMRA 2758511
	German standard soil Speyer 2.1 (non-sterile, slightly humus sand, pH 5.7, 0.65% OC) Field soil from Höfchen (non-sterile, sandy silt, pH 6.05, 2.17% OC), 22°C	< 2 days in two non-sterile soils (pH 5.7 and 6.05)	Important route of biotic transformation	PMRA 2758511 PMRA 2758506
	Sandy loam soil (pH 6.2)	10.18 hours TPs 2,2-dichloroacetaldehyde and dichloroethanol (each less than 12% of the applied), and 2,2-dichloroacetic acid (62.8% of applied at 48 hours post treatment)		PMRA 2480292

Process	**System**	**DT_{50}**	**Comments**	**Reference**
	Non-sterile Speyer 2.2 soil (loamy sand; pH 5.8, 2.42% OC)	Study used to determine positive identification of transformation products: Desmethyldichlorvos, 2,2-dichloroacetaldehyde, and 2,2-dichloroethanol 2,2-dichloroacetic acid at higher concentrations of dichlorvos and considered to be very short lived.		PMRA 2758511 PMRA 2758506
Anaerobic Soil Biotransformation	sandy loam soil (pH 6.8), 25°C	6.3 days	Important route of biotic transformation	PMRA 2480292
Aerobic Aquatic Biotransformation	orchard drainage ditch (%sand/silt/clay = 20.4/60.6/18.9; pH 7.1; 2.5% OC; 15,000 mg CaCO3/kg) reclaimed gravel pit (%sand/silt/clay = 73.8/14.6/11.6; pH 7.4; 0.8% OC; 11,500 mg CaCO3).	≤1 day	Important route of biotransformation	PMRA 2758511 PMRA 2758506
	ditch (Delf: %sand/silt/clay = 37.4/34.1/28.5; pH 7.3; 7.3% OM; 8700 mg CaCO3/kg) and a river (Odijk: %sand/silt/clay = 73.2/14/12.8; pH 7.4; 3.1% OM; 5100 mg CaCO3)	Ditch whole system = 0.52 days River whole system = 0.44 days		PMRA 2758506
Anaerobic Aquatic Biotransformation			No data available	

Table 4 Summary of Mobility of Dichlorvos

Process	Soil/location	Study $K_F/K_{om}/K_{oc}$	PMRA-converted K_{oc}[1]	Comment	Reference
Adsorption/desorption	Modelled value – parameters not stated	K_{oc} 150	same	High to very high mobility	PMRA 2758511
	Not stated	K_{oc} 36.9	same		PMRA 2480292
	loam sand	K_F/K_{om} 2/87	150 (using soil OM report as 4.3%)		PMRA 2758506
	Humic sand	K_F/K_{om} 4.2/98	169 (using soil OM reported as 2.3%)		
Soil column leaching	Sand-sandy loam soils with varying pH (5.2-7), %OC (0.6-2.6), and clay content (4-20%)	No detection of dichlorvos in leachate	same	Concluded that extensive hydrolysis and microbial transformation of dichlorvos may have occurred during leaching and prior to measurement	PMRA 2758511
	Sand soil, and sandy silt soil	No detection of dichlorvos in leachate. However, study reviewers determined a DT50 < 2 days, and likely < 1 day	same	Dichlorvos degraded very rapidly. Transformation product detected in leachate was 2,2, dichloroethanol, with a maximum of just under 10%. The transformation product desmethyldichlorvos was also detected, but at 0.7 to 0.9% after the first day only.	PMRA 2758506

[1] $K_d=K_{om}$ (%OM); $K_{oc}=K_d$/%OC, where %OC=%OM/1.72)

Table 5 Acute, Dietary, and Chronic Toxicity of Dichlorvos to Birds and Mammals

Species	Test Substance Purity	LD$_{50}$ (mg a.i./kg bw)	Classification	Reference
Acute oral toxicity - birds				
Mallard duck (*Anas platyrhynchos*)	93% (core for EPA, supplemental for Australia)	male 7.78 (6.0-10.1)	Very highly toxic	PMRA 2758511 PMRA 2480292
Japanese quail (*Coturnix c. japonica*)	NR (for information - Australia)	male 22 female 26	Highly toxic	PMRA 2758511

Species	Test Substance Purity	LD$_{50}$ (mg a.i./kg bw)	Classification	Reference
Quail (*Coturnix coturnix*)	96% (acceptable – Australia)	female 23.7	Highly toxic	
Domestic fowl (*Gallus domesticus*)	NR (for info – Australia)	chick 14.8	Highly toxic	
Ring-necked pheasant (*Phasianus colchicus*)	93% (core- EPA, supplemental – Australia)	male 11.3 (9.0-14.3)	Highly toxic	
Canary (*Serinus canarius*)	97.4% (acceptable- Australia)	female 2.5-10	Very highly toxic	
Common grackle (*Quiscalus quiscula*)	96% (acceptable- Australia)	13.3	Highly toxic	
Red-winged blackbird (*Agelaius phoeniceus*)	96% (acceptable- Australia)	male 13.3	Highly toxic	
House sparrow (*Passer domesticus*)	96% (acceptable- Australia)	17.8 (10.0-31.6)	Highly toxic	
Starling (*Sturnus vulgaris*)	96% (acceptable- Australia)	42.1	Highly toxic	
Common pigeon	96% (acceptable- Australia)	23.7 (13.3-42.1)	Highly toxic	
Bobwhite quail (*Colinus virginianus*)	96.5% (core- EPA)	8.8 (6.2-13.4)	Very highly toxic	PMRA 2480292
Dietary toxicity - birds				
Mallard duck (*Anas platyrhynchos*)	94.8% (core)	LC$_{50}$ >1317 (1043-1674) mg a.i./kg diet	slightly toxic	PMRA 2758511 PMRA 2480292
Mallard duck (*Anas platyrhynchos*)	94.8% (core)	LC$_{50}$ >5000 mg a.i./kg diet	practically non-toxic	
Japanese quail (*Coturnix c. japonica*)	94.8% (supplemental)	LC$_{50}$ = 298 (257-345) mg a.i./kg diet	highly toxic	
Ring-necked pheasant (*Phasianus colchicus*)	94.8% (core)	LC$_{50}$ = 568 (473-675) mg a.i./kg diet	moderately toxic	

Species	Test Substance Purity	LD_{50} (mg a.i./kg bw)	Classification	Reference
Chronic toxicity - birds				
Mallard (20 week dietary exposure)	98	NOEC=5 mg/kg, converted[2] to per unit body weight = 0.2828 (mg a.i./kg bw/d). Based on eggshell thickness, eggs laid, viable embryos, live three week embryos	N/A	PMRA 2480292
Northern bobwhite quail (20 week dietary exposure)		NOEC=30 mg/kg, converted[2] to per unit body weight = 3.185 (mg a.i./kg bw/d). Eggs laid, viable embryos and live three week embryos, normal hatchlings, fourteen day old survivors	N/A	
Acute oral toxicity - mammals				
Rat	Technical (% not specified)	LD_{50} = 80 mg/kg (m) LD_{50} = 56 mg/kg (f)	N/A	PMRA 2480292
Chronic toxicity - mammals				
Rat	98.3%	NOEC = 20 ppm (Fertility, pup weight), converted[3] to 2.57 mg/kg BW/d	N/A	PMRA 2480292

[1] 95% confidence limits indicated in parentheses

[2] endpoint times the food ingestion rate/body weight of test animals (i.e., NOEC or LOEC × FIR/BW). Default values are used for the FIR and BW - bobwhite quail FIR=18.9 g dry weight food/day, and BW = 178 g; mallard FIR = 61.2 g dry weight food/day, and BW = 1082 g

[3] endpoint times the food ingestion rate/body weight of test animals (i.e., NOEC or LOEC × FIR/BW). Default FIR and BW for the rat are 4.5 g dry weight food/day and 35 g, respectively

Table 6 Acute Toxicity of Dichlorvos to Aquatic Invertebrates

Species	Test Material and Method	Endpoint	Toxicity Classification	Reference
Waterflea (*Daphnia pulex*)	100% a.i. method not stated	48 h EC_{50} = 0.07 µg/L	Very highly toxic	PMRA 2480292
Waterflea (*Simocephalus serrulatus*)	100% a.i. method not stated	48 h EC_{50} = 0.28 µg/L	Very highly toxic	
Waterflea (*Simocephalus serrulatus*)	100% a.i.. method not stated	48 h EC_{50} = 0.26 µg/L	Very highly toxic	
Waterflea *Daphnia magna*	TGAI, static	48 h EC_{50} = 0.19 µg/L	very highly toxic	PMRA 2758511 PMRA 2758508
Waterflea *Daphnia magna*	TGAI, 97-98% , static	48 h EC_{50} = 0.19 µg/L	Very highly toxic	PMRA 2758508
Waterflea *Daphnia magna*	TGAI, 98%, conditions not reported	48 h EC_{50} = 0.085 µg/L	Very highly toxic	
Crayfish *Procambarus clarkii*	TGAI, static	48 h LC_{50} = 880 µg/L	highly toxic	PMRA 2758511
Freshwater prawn *Macrobrachiu m lamarrei*	not indicated	96 h LC_{50} = 881 µg/L	highly toxic	
Isopod *Alitropus typus*	TGAI, static	48 h LC_{50} = 9.25 µg/L	very highly toxic	
Water bug *Sigara substriata*	EC formulation, static	48 h LC_{50} = 65 µg/L	very highly toxic	
Water bug *Micronecta sedula*	EC formulation, static	48 h LC_{50} = 55 µg/L	very highly toxic	
Mayfly *Cloeon dipterum*	EC formulation, static	48 h LC_{50} = 28 µg/L	very highly toxic	
Dragonfly *Ortheretrum albistylum*	EC formulation, static	48 h LC_{50} = 14 µg/L	very highly toxic	
Dragonfly *Sympetrum frequens*	EC formulation, static	48 h LC_{50} = 100 µg/L	highly toxic	

Species	Test Material and Method	Endpoint	Toxicity Classification	Reference
Amphipod *Gammarus lacustris*	100%, static	96 h LC_{50} = 0.5 µg/L	very highly toxic	PMRA 1268985 PMRA 2758508

Table 7 Chronic Toxicity Endpoints for Freshwater Invertebrates

Species	% a.i.	21-day NOEC/LOEC (mg/L)	Endpoint Affected	Reference
Waterflea (*Daphnia magna*)	98	0.0000058/0.0000122	Egg production and growth (length and weight)	PMRA 2480292

Table 8 Acute Toxicity of Dichlorvos to Freshwater Fish

Species	Test Material and Method	Endpoint	Classification	Reference
Rainbow trout (*Oncorhynchus mykiss*)	100% active ingredient (a.i.)	24 h LC_{50} = 0.5	Highly toxic	PMRA 2480292
Rainbow trout (*Oncorhynchus mykiss*)	42% a.i. (formulated product)	96 h LC_{50} = 0.32 (=0.75 for formulated product)	Highly toxic for formulated product	
Lake trout (*Salvelinus namaycush*)	100% a.i.	96 h LC_{50} = 0.187	Highly toxic	
	100% a.i.	96 h LC_{50} = 0.183	Highly toxic	
Bluegill sunfish (*Lepomis macrochirus*)	98% a.i.	96 h LC_{50} = 0.869	Highly toxic	
Bluegill sunfish (*Lepomis macrochirus*)	42% a.i. (formulated product)	96 h LC_{50} 1.860 (= 4.3 for formulated product)	Moderately toxic for formulated product)	
Rainbow trout (*Oncorhynchus mykiss*)	555 g/L; static	96 h LC_{50} = 0.5 mg/L	highly toxic	PMRA 2758511
Cutthroat trout (*Salmo clarkii*)	100%, static	96 h LC_{50} = 0.17 (0.14-0.206) mg/L	highly toxic	
Lake trout (*Salvelinus namaycush*)	100%, static	96 h LC_{50} = 0.187 (0.11-0.32) mg/L	highly toxic	
Bluegill sunfish (*Lepomis macrochirus*)	Not indicated	96 h LC_{50} = 0.48 mg/L	highly toxic	

Species	Test Material and Method	Endpoint	Classification	Reference
Golden orfe (*Leuciscus idus melanotus*)	555 g/L; static	96 h LC$_{50}$ = 0.2 mg/L	highly toxic	
Tilapia mozambica	TGAI, static	96 h LC$_{50}$ = 1.4 - 1.9 mg/L	moderately toxic	
Common Carp (*Cyprinus carpio*)	TGAI, static	96 h LC$_{50}$ = 0.34 mg/L	highly toxic	
	500 g/L; static	96 h LC$_{50}$ = 1.15 mg/L	moderately toxic	
Java Carp (*Puntius gonionotus*)	500 g/L; static	96 h LC$_{50}$ = 1.85 mg/L	moderately toxic	
Mosquito fish (*Gambusia affinis*)	100%, static	96 h LC$_{50}$ = 5.27 (2.6-10.4) mg/L	moderately toxic	PMRA 1268985
Fathead minnow (*Pimephales promelas*)	100%, static	96 h LC$_{50}$ = 11.6 (7.8-17.2) mg/L	slightly toxic	
Snakehead (*Ophiopcephalus punctatus*)	Not indicated	96 h LC$_{50}$ = 2.3 mg/L	moderately toxic	
Singii (*Saccobranchus fossilis*)	Not indicated	96 h LC$_{50}$ = 6.6 mg/L	moderately toxic	
Walking catfish (*Clarias batrachus*)	Not indicated	96 h LC$_{50}$ = 8.9 mg/L	moderately toxic	
African catfish (*Mystus vittatus*)	Not indicated	96 h LC$_{50}$ = 0.5 mg/L	highly toxic	

Table 9 Acute Toxicity of Dichlorvos to Marine Aquatic Invertebrates

Species	Test Material and Method	Endpoint	Toxicity Category	Reference
Eastern oyster (shell deposition) (*Crassostrea virginica*)	Test method not stated; conducted with 98% a.i.	96 h EC$_{50}$ = 89.1 mg/L	Slightly toxic	PMRA 2480292
Eastern oyster (shell deposition) (*Crassostrea virginica*)	Test method not stated; conducted with 42% a.i. (formulated product)	96 h EC$_{50}$ = 0.92 mg/L (2.18 mg/L formulated product)	Moderately toxic for formulated product	

Species	**Test Material and Method**	**Endpoint**	**Toxicity Category**	**Reference**
Mysid (*Americamysis bahia*)	Test method not stated; conducted with 98% a.i.	96 h LC_{50} = 0.0191 mg/L	Very highly toxic	
Mysid (*Americamysis bahia*)	Test method not stated; conducted with 42% a.i. (formulated product)	96 h LC_{50} = 0.0187 mg/L (0.044 formulated product)	Very highly toxic for formulated product	
Lobster (*Homarus gammarus*)	static renewal	96 h LC_{50} = 0.0057mg/L	very highly toxic	PMRA 2758511
Lobster (*Homarus gammarus*)	static renewal	96 h LC_{50} = 0.0087 mg/L	very highly toxic	
Pink shrimp (*Palaemon serratus*)	not indicated	96 h LC_{50} = 0.006 mg/L	very highly toxic	
Barnacle nauplii	not indicated	96 h LC_{50} = 4.5 mg/L	moderately toxic	
Mussels (*Mytilus edulis*)	not indicated	24h LC_{50} = 1 mg/L	highly toxic	
Sand shrimp (*Crangon septemspinosa*)	N.R., static	96 h LC_{50} = 0.004 mg/L	very highly toxic	PMRA 1268985
Grass shrimp (*Palaemonetes vulgaris*)	N.R., static	96 h LC_{50} = 0.015 mg/L	very highly toxic	
Hermit crab (*Pagurus longicarpus*)	N.R., static	96 h LC_{50} = 0.045 mg/L	very highly toxic	
Blood clam (*Anadara granosa*)	Static renewal, 91.17% a.i.	96 h LC_{50} = 1.79 mg a.i./L (1.36-2.36)	Moderately toxic	PMRA 2758508

Table 10 Acute Toxicity of Dichlorvos to Marine Fish

Species	Test Material and Method	Endpoint	Toxicity Category	Reference
Sheepshead minnow (*Cyprinodon variegatus*)	Test method not stated; conducted with 98% a.i.	96 h LC_{50} = 7.35 mg/L	Moderately toxic	PMRA 2480292
Sheepshead minnow (*Cyprinodon variegatus*)	Test method not stated; conducted with 42.39% a.i. (formulated product)	96 h LC_{50} = 6.146 mg a.i./L (14.5 mg/L formulated product)	Moderately toxic for formulated product	
Herring (*Clupea harengus*)	500 EC formulation (50.84%)	96 h LC_{50} to larvae = 0.122 mg a.i./L	highly toxic	PMRA 2758511
Spot (*Leiostomus xanthurus*)	TGAI	96 h LC_{50} = 0.55 mg/L	highly toxic	
American eel (*Anguilla rostrata*)	Not indicated	96 h LC_{50} = 1.8 mg/L	moderately toxic	PMRA 1268985 PMRA 2758508
Mummichog (*Fundulus heteroclitus*)	Not indicated	96 h LC_{50} = 2.7 mg/L	moderately toxic	
Striped killifish (*Fundulus majalis*)	90%, static	96 h LC_{50} = 2.3 mg/L	moderately toxic	
Atlantic silverside (*Menidia menidia*)	Not indicated	96 h LC_{50} = 1.3 mg/L	moderately toxic	
Striped mullet (*Mugil cephalus*)	98%, flow-through	96 h LC_{50} = 0.23 mg/L	highly toxic	
Northern puffer (*Sphaeroidus maculatus*)	Not indicated	96 h LC_{50} = 2.3 mg/L	moderately toxic	
Bluehead (*Thalassoma bifasciatum*)	Not indicated	96 h LC_{50} = 1.4 mg/L	moderately toxic	

Table 11 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Dichlorvos Are criteria met?
CEPA toxic or CEPA toxic equivalent[1]	Yes	Yes
Predominantly anthropogenic[2]	Yes	Yes

TSMP Track 1 Criteria	**TSMP Track 1 Criterion value**		**Dichlorvos** **Are criteria met?**
Persistence[3]:	Soil	Half-life $\geq$ 182 days	No: <19.3 days
	Water	Half-life $\geq$ 182 days	Data not available
	Whole system (Water + Sediment)	Half-life $\geq$ 365 days	No: <1 day
	Air	Half-life $\geq$ 2 days or evidence of long range transport	Long range transport is not expected based on using the method of Atkinson and the Atmospheric Oxidation Program (v.1.86) to estimate photochemical reaction with hydroxyl radicals, an atmospheric half-life of 13-20 hours was calculated.
Bioaccumulation[4]	Log $K_{OW} \geq 5$		No = 1.47
	BCF $\geq$ 5000		0.4-1.2
	BAF $\geq$ 5000		Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			**No, does not meet all TSMP Track 1 criteria.**

[1] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[2] The policy considers a substance "predominantly anthropogenic" if, based on expert judgment, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[3] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[4] The log L_{ow} and/or BCF and/or BAF are preferred over log K_{ow}.

Appendix X Label Amendments for Products Containing Dichlorvos

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the following label statements. **Note:** The following information is divided according to product type. Each section should be read carefully and appropriate changes should be made to product labels.

I) TECHNICAL GRADE AND COMMERCIAL CLASS PRODUCTS

a. Based on the toxicological assessments, the both of technical and commercial class product label text should be expanded and/or standardized as follows:

- Toxicology Information

"Dichlorvos is a cholinesterase inhibitor. Typical symptoms of overexposure to cholinesterase inhibitors include headache, nausea, dizziness, sweating, salivation, runny nose and eyes. This may progress to muscle twitching, weakness, tremor, incoordination, vomiting, abdominal cramps and diarrhea in more serious poisonings. A life-threatening poisoning is signified by loss of consciousness, incontinence, convulsions and respiratory depression with a secondary cardiovascular component. Treat symptomatically. If exposed, plasma and red blood cell cholinesterase tests may indicate degree of exposure (baseline data are useful). Atropine, only by injection, is the preferable antidote. Oximes, such as Pralidoxime Chloride, may be therapeutic if used early; however, use only in conjunction with atropine. In cases of severe acute poisoning, use antidotes immediately after establishing an open airway and respiration. With oral exposure,

- the decision of whether to induce vomiting or not should be made by an attending physician".

b. For the technical grade active ingredient product label, include the following:

Under ENVIRONMENTAL PRECAUTIONS, add the following:
"TOXIC to aquatic organisms."

Under PRECAUTIONS, add the following:
"DO NOT discharge effluent containing this product into sewer systems, lakes, streams, ponds, estuaries, oceans or other waters."

Under DISPOSAL, add the following:
"Canadian manufacturers should dispose of unwanted active ingredients and containers in accordance with municipal or provincial regulations. For additional details and clean-up of spills, contact the manufacturer or the provincial regulatory agency."

II) DOMESTIC-CLASS PRODUCTS

a. **The following statement must be added to the primary panel of all domestic pest strip products:**

"DO NOT USE in inhabited homes, including in attics, crawl spaces, and garages."

"DO NOT USE in commercial areas, including animal and other farm buildings, milk rooms, motels, restaurants, food processing plants, industrial and commercial locations, kennels, garbage storage areas and containers, and similar enclosed spaces."

"For use only in unoccupied structures, provided that they are continuously unoccupied for at least 4 months immediately following placement of the pest strip, such as vacation homes, cabins, mobile homes, and boats."

b. **Based on the toxicological assessments, the label text should be expanded and/or standardized as follows:**

Toxicology Information

"This product contains a pesticide that is a cholinesterase inhibitor (anti-cholinesterase compound). Symptoms of human poisoning may include headache, weakness, sweating, blurred vision, nausea and diarrhea. Obtain medical attention or call a poison control centre at once. Atropine is antidotal."

c. **Under a new or existing heading titled ENVIRONMENTAL PRECAUTIONS, add the following:**

"Toxic to aquatic organisms
Toxic to birds and small wild mammals"

d. **Under a STORAGE heading, add the following:**

"To prevent contamination store this product away from food or feed."

e. **Under DISPOSAL, add the following:**

"DO NOT reuse the empty containers. Dispose in household garbage.
Unused or partially used products should be disposed at provincially or municipally designated hazardous waste disposal sites."

III) COMMERCIAL-CLASS PRODUCTS

1. As the following uses are proposed for cancellation or not supported by the registrant, all references to these uses would be removed from all end-use product labels:

- greenhouse cucumbers and tomatoes
- greenhouse cut flower ornamentals
- outdoor mosquito control
- outdoor residential living area
- mushroom houses.

2. PRECAUTIONS

Personal Protective Equipment

a. For greenhouse potted ornamentals (that is, non-cut flowers) and animal buildings, the following label statements must be added:

"For use with automatic application equipment only. Individuals MUST not be present in the entire enclosed area during application. DO NOT APPLY with handheld equipment or handheld foggers."

"Wear coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, and chemical-resistant footwear during mixing, loading, clean-up and repair. In addition, a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides or a NIOSH approved canister approved for pesticides, MUST be worn."

b. For tobacco storage, the following label statements must be added:

"For use with automatic application equipment only. Individuals MUST not be present in the entire enclosed area during application. DO NOT APPLY with handheld equipment or handheld foggers."

"Limit the amount handed per day to 1.14 kg ai per person."

"Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and chemical-resistant footwear during mixing, loading, clean-up and repair. In addition, a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister for pesticides, MUST be worn."

c. For food processing plants, industrial plants, warehouses, theaters, the following label statements must be added:

"Limit the amount handled per day to 1.14 kg ai per person."

"Wear chemical-resistant coveralls over a long-sleeved shirt, long pants, chemical-resistant gloves, socks, and chemical-resistant footwear during mixing, loading, clean-up and repair. In addition, a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister for pesticides, MUST be worn."

d. For outdoor commercial pest strips (that is, insecticidal traps in fruit and vegetable crops), the following statements must be added:

"Wear chemical-resistant gloves, and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides when opening insect traps and for disposal of the pest strip."

3. DIRECTIONS FOR USE

a For all product labels (excluding pest strips), add the following:

"DO NOT contaminate irrigation or drinking water supplies or aquatic habitats by cleaning of equipment or disposal of wastes.

DO NOT apply by air."

b. For greenhouse potted ornamentals, the following label statement must be added:

i. Use Precautions

"For use on potted ornamentals only. DO NOT use on cut flowers."

ii. Under ENVIRONMENTAL PRECAUTIONS:

"Greenhouse use: Toxic to bees and other beneficial insects. May harm bees and other beneficial insects, including those used in greenhouse production. Do not apply when bees or other beneficial insects are foraging in the treatment area."

iii Under DIRECTIONS FOR USE:

"DO NOT allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters."

4. Restricted-Entry Interval

a. For greenhouse potted ornamentals, tobacco storage, animal buildings, food processing plants, industrial plants, warehouses, and theaters, the following label statement must be added:

"Do not enter or allow workers or other individuals to enter during the restricted entry interval of 4 days. Entry into treated areas MUST only occur after full ventilation. Ventilation is defined as:

- 10 air exchanges are completed; or
- 2 hours of ventilation using fans or other mechanical ventilating systems; or
- 4 hours of ventilation using vents, windows or other passive ventilation; or
- 11 hours with no ventilation followed by 1 hour of mechanical ventilation; or
- 11 hours of no ventilation followed by 2 hours of passive ventilation."

"Due to inhalation risk concerns, entry before 4 days is not permitted, including for non-hand labour tasks or short tasks such as turning on a light switch."

5. Under a new or existing heading titled ENVIRONMENTAL PRECAUTIONS, add the following:

"Toxic to aquatic organisms"
"Toxic to birds and small wild mammals"

To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil, or clay.

Avoid application when heavy rain is forecast.

Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

6. Under a STORAGE heading, add the following:

"To prevent contamination store this product away from food or feed."

7. OTHER REQUIREMENTS

a. For all products containing aromatic petroleum distillates, add the following:

This product contains (an) active ingredient(s) and aromatic petroleum distillates which are toxic to aquatic organisms.

b. Should the uses for outdoor surface spray and fogging remain registered after public consultation, the following statements would be required.

i. For all product labels with outdoor uses, add the following:

Under a new or existing heading titled ENVIRONMENTAL PRECAUTIONS, add the following:

Outdoor areas: Toxic to bees. Avoid application around blooming plants. Toxic to beneficial insects. Minimize exposure to non-target areas.

ii. And for products with outdoor ULV/fogging uses, add this additional information:

ULV / fogging: Toxic to bees and beneficial insects. Applications are typically made during the cooler hours of the night or early mornings which will minimize exposure to foraging bees and beneficial insects.

c. **Should the uses for greenhouse tomato, cucumber or cut flowers remain registered after public consultation, the following statements would be required.**

i. Under ENVIRONMENTAL PRECAUTIONS:

“Greenhouse use: Toxic to bees and other beneficial insects. May harm bees and other beneficial insects, including those used in greenhouse production. Do not apply when bees or other beneficial insects are foraging in the treatment area.”

ii. Under DIRECTIONS FOR USE:

“DO NOT allow effluent or runoff from greenhouses containing this product to enter lakes, streams, ponds or other waters.”

References

Information Considered in the Chemistry Assessment

A. Studies /Information Submitted by the Registrant

PMRA Document Number	Reference
2456730	1997. DDVP Technical: Preliminary Analysis, Product Identity and Impurity Identification. DACO: 2.13 CBI
2456732	2007. Preliminary Analysis of DDVP Technical. DACO: 2.13 CBI
2495066	2009. Development and Validation of an Analytical Method for the Analysis of [CBI Removed] in DDVP Technical. DACO: 2.13.1 CBI
2497739	2015. Production Process for Dichlorvos Technical Grade Insecticide. DACO: 2.11 CBI
2512868	2015. Qualitative Characterization of [CBI Removed] Standard, DACO: 2.13.2 CBI
2512869	2015. Analysis of [CBI Removed] Standard, DACO: 2.13.2
2527742	2015. Enforcement Analytical Method for the Determination of [CBI Removed] in DDVP Technical, DACO: 2.13.1 CBI
2527743	2015. Enforcement Analytical Method for the Determination of [CBI Removed] in DDVP Technical, DACO: 2.13.1 CBI
2554160	2015. Materials Used for Production of Dichlorvos Technical Grade Insecticide, DACO: 2.11.2 CBI
2554161	2015. Formation of Impurities: Dichlorvos Insecticide Technical Grade, DACO: 2.11.4 CBI
2554162	2015. Quality Control Verification of Dichlorvos (DDVP) Technical Composition, DACO: 2.13.1 CBI
2675391	2016. DDVP Method Validation for the Quantification of Active Substance, DACO: 2.13.1 CBI
2675392	2016. DDVP Method Validation for the Quantification of Impurity Components, DACO: 2.13.1 CBI
2675393	2016. DDVP Batch Analysis, DACO: 2.13.3 CBI
2690742	2016. DDVP Method Validation, DACO: 2.13.4 CBI
2690743	2016. DDVP Method Validation, DACO: 2.13.4 CBI
2690744	2016. DDVP Batch Analysis, DACO: 2.13.4 CBI

Information Considered for the Toxicological Risk Assessment

A. Studies /Information Submitted by the Registrant

PMRA Document Number	Reference
1267322	1997. Dichlorvos: A study to investigate erythrocyte cholinesterase inhibition following oral administration to healthy male volunteers. Laboratory Report No. CTL/P/5251, Study No. XH5170, February 3rd, 1997. Unpublished Study. DACO 4.8.
1267323	1997. First Supplement to Dichlorvos: A study to investigate erythrocyte cholinesterase inhibition following oral administration to healthy male volunteers. Laboratory Report No. CTL/P/5251, Study No. XH5170, October 8th, 1997. Unpublished Study. DACO 4.8.
1267324	1997. Dichlorvos: A single blind, placebo controlled, randomised study to investigate the effects of multiple oral dosing on erythrocyte cholinesterase inhibition in healthy male volunteers. Laboratory Report No. CTL/P/5392, Study No. XH6063, March 24th, 1997. Unpublished Study. DACO 4.8.
1267325	1997. First Supplement to Dichlorvos: A single blind, placebo controlled, randomised study to investigate the effects of multiple oral dosing of dichlorvos on erythrocyte cholinesterase inhibition in healthy male volunteers. Laboratory Report No. CTL/P/5392, Study No. XH6063, October 9th, 1997. Unpublished Study. DACO 4.8.
1267326	1997. Dichlorvos: A study to investigate the effect of a single oral dose on erythrocyte cholinesterase inhibition in healthy male volunteers. Laboratory Report No. CTL/P/5393, Study No. XH6064, March 25th, 1997. Unpublished Study. DACO 4.8.
1267327	1997. First Supplement to Dichlorvos: A study to investigate the effect of a single oral dose of Dichlorvos on erythrocyte inhibition in healthy male volunteers. Laboratory Report No. CTL/P/5393, Study No. XH6064, October 8th, 1997. Unpublished Study. DACO 4.8.
2502260	2003. Dichlorvos: Repeat Dose Cholinesterase Inhibition Study in Pre-weaning and Young Adult Rats. Laboratory Report No. CTL/KR1490/Regulatory/Report, Study No. KR1490. October 24th, 2003. Unpublished Study. DACO 4.5.12.
2502264	2002.Dichlorvos (DDVP): Acute Cholinesterase Inhibition Study in Pre-weaning rats. Laboratory Report No.: CTL/AR7147/ Regulatory/Report, Study No.: AR7147. November 22nd, 2002. Unpublished Study. DACO 4.5.12.
2502261	2002. Dichlorvos (DDVP): Second Acute Cholinesterase Inhibition Study in Rats. Laboratory Report No. CTL/AR7126/ Regulatory/Report, Study No. AR7126. June 19th, 2002. Unpublished Study. DACO 4.5.12.
2502262	2002. Dichlorvos (DDVP): Third Acute Cholinesterase Inhibition Study in Rats. Laboratory Report No. CTL/AR7138/Regulatory/Report, Study No. AR7138. June 26th, 2002. Unpublished Study. DACO 4.5.12.
2541047	1993. A Subchronic (13 week) Neurotoxicity Study of Dichlorvos in Rats, Volume 1 of 4. Laboratory Study No. WIL-188004. September 30th, 1993. Unpublished Study. DACO 4.5.13.

PMRA Document Number	Reference
2541048	1993. A Subchronic (13 week) Neurotoxicity Study of Dichlorvos in Rats, Volume 2 of 4. Laboratory Study No. WIL-188004. September 30th, 1993. Unpublished Study. DACO 4.5.13.
2541049	1993. A Subchronic (13 week) Neurotoxicity Study of Dichlorvos in Rats, Volume 3 of 4. Laboratory Study No. WIL-188004. September 30th, 1993. Unpublished Study. DACO 4.5.13.
2541050	1993. A Subchronic (13 week) Neurotoxicity Study of Dichlorvos in Rats, Volume 4 of 4. Laboratory Study No. WIL-188004. September 30th, 1993. Unpublished Study. DACO 4.5.13.
1267197, 1267198	2003. Developmental neurotoxicity study in rats. Laboratory Report No. CTL/RR0886/ Regulatory/Report, Study No. RR0886. November 10th, 2003. Unpublished study. DACO 4.5.14.
1267196	2003.Preliminary developmental neurotoxicity study in rats. Laboratory Report No. CTL/RR00885/Regulatory/Report, Study No. RR00885. October 13th, 2003. Unpublished study. DACO 4.5.14.
1267202, 1267205	2004. Supplemental developmental neurotoxicity study in rats. Laboratory Report No. TL/RR0988/Regulatory/Report, Study No. RR0988. January 28th, 2004. Unpublished study. DACO 4.5.14.

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
2489912	2009. Hematotoxic and hepatotoxic effects of dichlorvos at sublethal dosages in rats, Environmental Toxicology, 24(2): 128-132. DACO 4.8
2489916	2004. Prenatal exposure to dichlorvos: physical and behavioral effects on rat offspring, Neurotoxicology and Teratology, 26(4): 607-614. DACO 4.8
2489923	2008. Dichlorvos-induced hepatotoxicity in rats and the protective effects of vitamins C and E, Environmental Toxicology and Pharmacology, 26(3): 355-361. DACO 4.8
2489910	2002. Effects of currently used pesticides in assays for estrogenicity, androgenicity and aromatase activity in vitro, Toxicology and Applied Pharmacology, 179(1): 1-12. DACO 4.8
2489926	2007. In vitro induction of cytotoxicity and DNA strand breaks in CHO cells exposed to cypermethrin, pendimethalin and dichlorvos, Toxicology in vitro: an international journal published in association with BIBRA, 21(8):1409-1418. DACO 4.5.6
2489927	2010. Decreased sperm motility in rats orally exposed to single or mixed pesticides, Journal of Toxicology and Environmental Health, Part A, 73(13-14): 991-1002. DACO 4.8

PMRA Document Number	Reference
2489924	2009. Broken sperm, cytoplasmic droplets and reduced sperm motility are principal markers of decreased sperm quality due to organophosphorus pesticides in rats, Journal of Occupational Health, 51(6):478-487. DACO 4.8
2489913	2012. Dichlorvos-induced testicular toxicity in male rats and the protective role of vitamins C and E, Experimental and Toxicologic Pathology, 64(7-8): 821-830. DACO 4.8
2489918	2006. Aneuploidy-inducing capacity of two widely used pesticides, Carcinogenesis, 27(12): 2511-2518. DACO 4.5.6
2489921	2014. Genotoxicity of dichlorvos in strains of Drosophila melanogaster defective in DNA repair, Mutation Research. Genetic Toxicology and Environmental Mutagenesis, 766: 35-41. DACO 4.5.7
2489922	2013. Assessment of genotoxic potential of the insecticide Dichlorvos using cytogenetic assay, Interdisciplinary Toxicology, 6(2): 77-82. DACO 4.5.6
2489915	2008, Dichlorvos exposure and human cancer risk: results from the Agricultural Health Study, Cancer Causes and Control, 19(1): 59-65. DACO 4.8
2489919	2003. Prostate cancer risk in California farm workers, Journal of Occupational and Environmental Medicine, 45(3): 249-258. DACO 4.8
2489914	2004. Cancer risk and parental pesticide application in children of Agricultural Health Study participants, Environmental Health Perspectives, 112(5): 631-635. DACO 4.8
2480298	1975. The distribution of Dichlorvos in the tissues of mammals after its inhalation or intravenous administration, Toxicology and Applied Pharmacology, 31: 243-253. DACO 4.5.9
2480297	1975. The activities of some esterases of the rat brain after intoxication by organophosphate insecticides, Dichlorvos and Trichlorphon, Neuropatologia Polska, 13(3-4): 455-462. DACO 4.8
2480299	1981. Estimation of genetic risks of alkylating agents. V. Methylation of DNA in the mouse by DDVP (2,2-dichlorovinyl dimethyl phosphate), Hereditas, 94: 73-76. DACO 4.8
2489925	2006. Endometrial damage and apoptosis in rats induced by dichlorvos and ameliorating effect of antioxidant vitamins E and C. Reproductive Toxicology, 22: 783–790. DACO 4.8
2489909	2000. Retention of cytoplasmic droplet by rat cauda epididymal spermatozoa after treatment with cytotoxic and xenobiotic agents. Journal of Reproduction and Fertility, 120: 385–390. DACO 4.8
2534673	1994. Investigations of the genotoxicity and cell proliferative activity of dichlorvos in mouse forestomach. Toxicology, 92: 203-215. DACO 4.8
2534672	1977. In vivo alkylation studies with dichlorvos at practical use concentrations. Chemico-Biological Interactions, 19: 25-46. DACO 4.5.7
2544132	2000. Dichlorvos and Carcinogenicity: A systematic Approach to a Regulatory Decision. Regulatory Toxicology and Pharmacology, 31: 13-21. DACO 12.5.4
2573208	1980. The Effect of DDVP, an Organophosphorus Pesticide on the Humoral and Cell-Mediated Immunity of Rabbits. Archives of Toxicology, Suppl. 4: 171-174. DACO 4.8

PMRA Document Number	Reference
2573217	1971. Effects of Dichlorvos on Blood Cholinesterase Activity in Dogs. Journal of the American Veterinary Medicine Association, 158(4): 457-461. DACO 4.8
2573218	1978. Studies on the Immunosuppressive Effect of Organochlorine and Organophospheric Pesticides in Subactue Experiments, Journal of Hygiene, Epidemiology, Microbiology and Immunology, 22(1): 115-122. DACO 4.8
2574312	1993. Pesticide Exposures and Multiple Myeloma in Iowa Men, Cancer Causes and Control, 4(2): 153-156. DACO 4.8
2574314	1992. Pesticides and other agricultural risk factors for Non-Hodgkin's Lymphoma among Men in Iowa and Minnesota, Cancer Research, 52: 2447-2455. DACO 4.8
2574315	1990. Pesticide Exposures and other Agricultural Risk Factors for Leukemia among men in Iowa and Minnesota, Cancer Research, 50: 6585-6591. DACO 4.8
2574316	2008. Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003, American Journal of Epidemiology, 167(10): 1235-1246. DACO 4.8
2533059	2003. Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. American Journal of Epidemiology, 157: 800-814. DACO 4.8
2576215	2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men, Occupational and Environmental Medicine, 60: E11. DACO 4.8
2690526	1990. A case-controls study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology, 1990, 1: 349-56. DACO 4.8
2690525	1986. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. The Journal of the American Medical Association, 256(9): 1141-1147. DACO 4.8
2506314	1995. Pesticide Safety Directorate (PSD). Evaluation of Fully Approved or Provisionally Approved Products, Evaluation on Dichlorvos: Review of its Use in Public Hygiene and Amateur Insecticides. DACO 12.5.4
2506312, 2506313	2000. National Registration Authority for Agricultural and Veterinary Chemicals (NRA). NRA Review Series 00.4. The Review of Dichlorvos, Volumes I and II. DACO 12.5.4
2500808	1998. California Environmental Protection Agency (Cal EPA). Department of Pesticide Regulation, Medical Toxicology Branch. Dichlorvos (DDVP) Second Addendum to Risk Characterization Document. DACO. 12.5.4
2480292	2006. United States Environmental Protection Agency (US EPA). Reregistration Eligibility Decision for Dichlorvos (DDVP). DACO 12.5.4
2480293	2011. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Dichlorvos: Pesticide Residues in Food - 2011 Evaluation, Part II. Toxicology. DACO 12.5.4
2480294	2011. Australian Pesticides and Veterinary Medicines Authority (APVMA). Dichlorvos final review report and regulatory decision. The reconsideration of the active constituent dichlorvos, registrations of products containing dichlorvos, and approvals of their associated labels. DACO 12.5.4
2480295	2006. European Food Safety Authority (EFSA). Scientific Report. Conclusion on the peer review of Dichlorvos - Conclusion regarding the peer review of the pesticide risk assessment of the active substance Dichlorvos. DACO 12.5.4

PMRA Document Number	Reference
2480296	1991. International Agency for Research on Cancer (IARC). Summaries and Evaluations, Dichlorvos (Group 2B), 53: 267. DACO 12.5.4
2489911	2008. California Environmental Protection Agency (Cal EPA). Department of Pesticide Regulation, Medical Toxicology Branch. Summary of Toxicology Data DDVP. DACO. 12.5.4
2534676	1993. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Dichlorvos: Pesticide Residues in Food - 1993 Evaluation, Part II. Toxicology. DACO 12.5.4
2534675	1989. World Health Organization (WHO). International Programme on Chemical Safety, Environmental Health Criteria 79: Dichlorvos. DACO 12.5.4

ii) Unpublished Information

PMRA Document Number	Reference
2502268	2002. Data Evaluation Record, Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, March 31st, 2003. Dichlorvos (DDVP): Acute Cholinesterase Inhibition Study in Pre-weaning rats. Laboratory Report No.: CTL/AR7147/ Regulatory/Report, Study No.: AR7147. November 22nd, 2002. MRID No. 45842301. Unpublished Study. DACO: 4.5.12.
2502265	2002. Data Evaluation Record, Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, May 19th, 2003. Dichlorvos (DDVP): Second Acute Cholinesterase Inhibition Study in Rats. Laboratory Report No.: CTL/AR7126/ Regulatory/Report, Study No.: AR7126. June 19th, 2002. MRID No. 45805702. Unpublished Study. DACO: 4.5.12.
2502266	2002. Data Evaluation Record, Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, May 19th, 2003.Dichlorvos (DDVP): Third Acute Cholinesterase Inhibition Study in Rats. Laboratory Report No.: CTL/AR7138/ Regulatory/Report, Study No.: AR7138. June 26th, 2002. MRID No. 45805703. Unpublished Study. DACO: 4.5.12.
1262648	2005. Data Evaluation Record, Health Effects Division, Office of Pesticide Programs, United States Environmental Protection Agency, November 3rd, 2005. Re-evaluation of DNT Studies for DDVP. DACO: 4.5.14.

Information Considered in the Dietary Assessment

A. List of Studies/Information Submitted by Registrant

None

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
1566245	2008. Dichlorvos Re-evaluation Note, REV2008-04-Dichlorvos Interim Measures. March 6, 2008
	2013. Commission Regulation (EU) No 73/2013, January 25, 2013. http://extwprlegs1.fao.org/docs/pdf/eur119567.pdf Accessed July 10, 2017. DACO: 12.5
	2001. USEPA. General Principles for Performing Aggregate Exposure and Risk Assessments. November 28, 2001. https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/034401/034401-168.pdf. Accessed July 10, 2017. DACO: 12.5
2779900	1999. USEPA Memo D253929. Acute Probabilistic Dietary Exposure Estimates for Naled. June 8, 1999. DACO: 12.5
	1999. USEPA Memo D260129. Naled. Revised HED Risk Assessment for RED. October 12, 1999. https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/034401/034401-168.pdf. Accessed July 10, 2017. DACO: 12.5
	1995. USEPA Memo. Dietary Exposure Analyses for Naled in Support of the Reregistration Eligibility Decision. April 7, 1995. https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-034401_7-Apr-95_152.pdf. Accessed July 10, 2017. DACO: 12.5
	2007. USEPA Memo. D340492. Dichlorvos Acute, Probabilistic and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Reregistration Eligibility Decision. November 8, 2007. https://www.regulations.gov/document?D=EPA-HQ-OPP-2006-0396-0098. Accessed July 10, 2017. DACO: 12.5
	1994. USEPA Memo. D199979. Dichlorvos Reregistration Case No. 310 Processing studies on field corn, wheat, rice, cottonseed and soybeans. MRID 42993501. July 18, 1994. https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/084001/084001-36.pdf. Accessed July 10, 2017. DACO: 12.5
2779898	1998. USEPA Memo. Dichlorvos Product and Residue Chemistry Chapters for the Reregistration Eligibility Document. D238942. April 9, 1998. DACO: 12.5
2779901	1999. USEPA Memo. Naled. PC Code: 034401. Case No. 0092 Dietary Risk Assessment. D253670. March 10, 1999. DACO: 12.5

PMRA Document Number	Reference
2779899	1999. USEPA Memo. Naled. PC Code: 034401. Case No. 0092 Chronic anticipated Residues for dietary exposure analysis. D253669. March 5, 1999. DACO: 12.5
	1995. USEPA Memo. CSR PC-034401. Dietary Exposure Analyses for Naled in Support of the Reregistration Eligibility Decision Document. April 7, 1995. https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-034401_7-Apr-95_152.pdf. Accessed July 10, 2017. DACO: 12.5
	2008. USEPA document. Naled Screening Level Usage Analysis (SLUA). August 27, 2008. EPA-HQ-OPP-2009-0053-0007. https://www.regulations.gov/document?D=EPA-HQ-OPP-2009-0053-0007. Accessed July 10, 2017. DACO: 12.5

Information Considered in the Occupational and Non-occupational Assessment

A. **List of Studies/Information Submitted by the Registrant/Provided by Task Force**

Studies/Information Provided by the Registrant

PMRA Document Number	Reference
2586571	2015. DDVP Pest Strip Closet Use Under Controlled Apartment Conditions. Study ID: PRS11006. June 6, 2015. Unpublished. DACO: 5.10

Studies/Information Provided by the Task Force

PMRA Document Number	Reference
2115788	2008. Agricultural Reentry Task Force (ARTF). Data Submitted by the ARTF to Support Revision of Agricultural Transfer Coefficients. Submission# 2006-0257. DACO: 5.6
2572743	2014. Agricultural Handler Exposure Task Force (AHETF).AHETF Scenario Monograph: Open Cab Airblast Application of Liquid Sprays. Report Number AHE1006. October 20, 2014. DACO: 5.3
2572745	2015. Agricultural Handler Exposure Task Force (AHETF). Open Pour Mixing and Loading of Liquid Formulations. Report Number AHE1003-1. March 31, 2015. DACO: 5.3
	2005. Consumer Specialty Products Association (CSPA). Pyrethrin Steering Committee/Joint Venture and Piperonyl Butoxide Task Force II. Discussion Paper: Intermittent Aerosols, Residential Mosquito Misters, and Dairy Barn Misters. DACO: 5.2

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
2779894	1996. Mannien, A., Kangas, J., Tuomainen, A., and R. Tahvonen. Exposure to Insecticides in the Use of Cold Fog Generators in Greenhouses. Toxicological and Environmental Chemistry, 57: 213-24. DACO: 5.9A, 5.10
2779895	2000a. US EPA. HED Revised Preliminary Human Health Risk Assessment for Dichlorvos. Case No. 0104. D267106. Chemical No. 057901. DACO: 12.5.5
2779896	2000b. US EPA. Revision of Exposure Assessment for Dichlorvos (DDVP) Applied to Warehouses and Food Processing Plants. PC Code 084001. D266572. June 7, 2000. DACO: 12.5.5
2409268	2012. US EPA. Standard Operating Procedures for Residential Pesticide Exposure Assessment. EPA: Washington, DC. Revised October 2012. DACO: 12.5.5
2715322	2011. US EPA. Exposure Factors Handbook. EPA/600/R-090/052F. EPA: Washington, DC. September 2011. DACO: 5.2

ii) Unpublished Information

PMRA Document Number	Reference
2779897	1993. US EPA. Review of Exposure Monitoring Study for Use of DDVP in Food Processing Establishments. December 6th, 1993. DACO: 12.5.5
189789	1990. US EPA. Data Evaluation Report - Dermal Absorption of Dichlorvos in Rats.Laboratory Project ID 4615. Mar 23, 1990. MRID 414352-01. DACO: 12.5.5

Information Considered in the Environmental Assessment

A. List of Studies/Information Submitted by the Registrant

None

B. Additional Information Considered

i) Published Information

PMRA Document Number	Reference
2480292	2006. United States Environmental Protection Agency. Reregistration Eligibility Decision for Dichlorvos (DDVP). DACO: 12.5

2758506	2005. Ministry of Health, Department of Food, Nutrition, and Veterinary Public Health (Italy). Draft Assessment Report (DAR) public version- Initial risk assessment provided by the rapporteur member state Italy for the existing active substance dichlorvos. Volume 3. Annex B, B.8. Fate and behaviour in the environment. June 2005. DACO: 12.5
2758508	2005. Ministry of Health, Department of Food, Nutrition, and Veterinary Public Health (Italy). Draft Assessment Report (DAR) public version- Initial risk assessment provided by the rapporteur member state Italy for the existing active substance dichlorvos. Volume 3. Annex B. B.9. Ecotoxicology. June 2005. DACO: 12.5
2758511	2000. National Registration Authority for Agricultural and Veterinary Chemicals. Draft Review of Dichlorvos. Volume 1. June 2000. Australia. DACO: 12.5
1268985	1989. WHO. Dichlorvos. Environmental Health Criteria 79. World Health Organisation. Geneva, Switzerland. DACO: 12.5.4, 12.5.7, 12.5.8, 12.5.9